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OBSERVATIONS ON PARTIAL REMOVAL OF THE POST-CENTRAL GYRUS FOR PAIN

BY

WALPOLE LEWIN and C. G. PHILLIPS

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The role of the cerebral cortex in the conscious appreciation of pain has interested neurologists for many years. Head and Holmes (1911) considered that pain entered consciousness at thalamic level, and more recently Penfield (1947) stated that ". . . no removal of cortex anywhere can prevent pain from being felt and only very rarely does a patient use the word pain to describe the result of cortical stimulation", and, he goes on, "it is obvious therefore that the pathway of pain conduction reaches the thalamus and consciousness without essential conduction to the cortex". Adrian (1941) found that no impulses reached the sensory cortex in response to noxious or thermal stimulation at the periphery in the rabbit, cat, and monkey. On the other hand, a considerable body of evidence would suggest that there is central representation of pain in the cortex, and this work has been summarized recently by Marshall (1951) who, in presenting further evidence from 11 cases of cortical wounds followed by impairment of pain and temperature sense, advanced the hypothesis that the final elaboration of sensory impulses depends on mutual activation of thalamus and cortex.

Electrical stimulation of the cortex has yielded equivocal results. In Cushing's (1909) two cases stimulation of the post-central gyrus was painless, and Foerster (1936) reported paraesthesiae but seldom pain. Penfield and Boldrey (1937) recorded only 11 instances out of well over 800 responses to electrical stimulation where the word "pain" had been used by the patient to describe the cortical sensation. Recently, however, Horrax (1946) stimulated the post-central gyrus in four patients suffering from painful states and elicited pain in three. To explain the apparent discrepancy between his results and those of Penfield and Boldrey, Horrax concluded that he was probably using too strong a current, since in the motor cortex the same current caused convulsions. Stone (1950) also recorded one case where stimulation of the sensory cortex produced pain in the phantom leg.

In this paper we wish to record three cases in which partial resection of the post-central gyrus was undertaken for the relief of pain. In the first patient the pain developed during an unusual, prolonged, sensory painful aura in traumatic epilepsy, the second patient had intractable pain in a phantom foot, and the third had a painful thigh stump. In all three, electrical stimulation of the appropriate area of the post-central gyrus reproduced the pain complained of by the patient and relief followed the removal of this area of cortex.

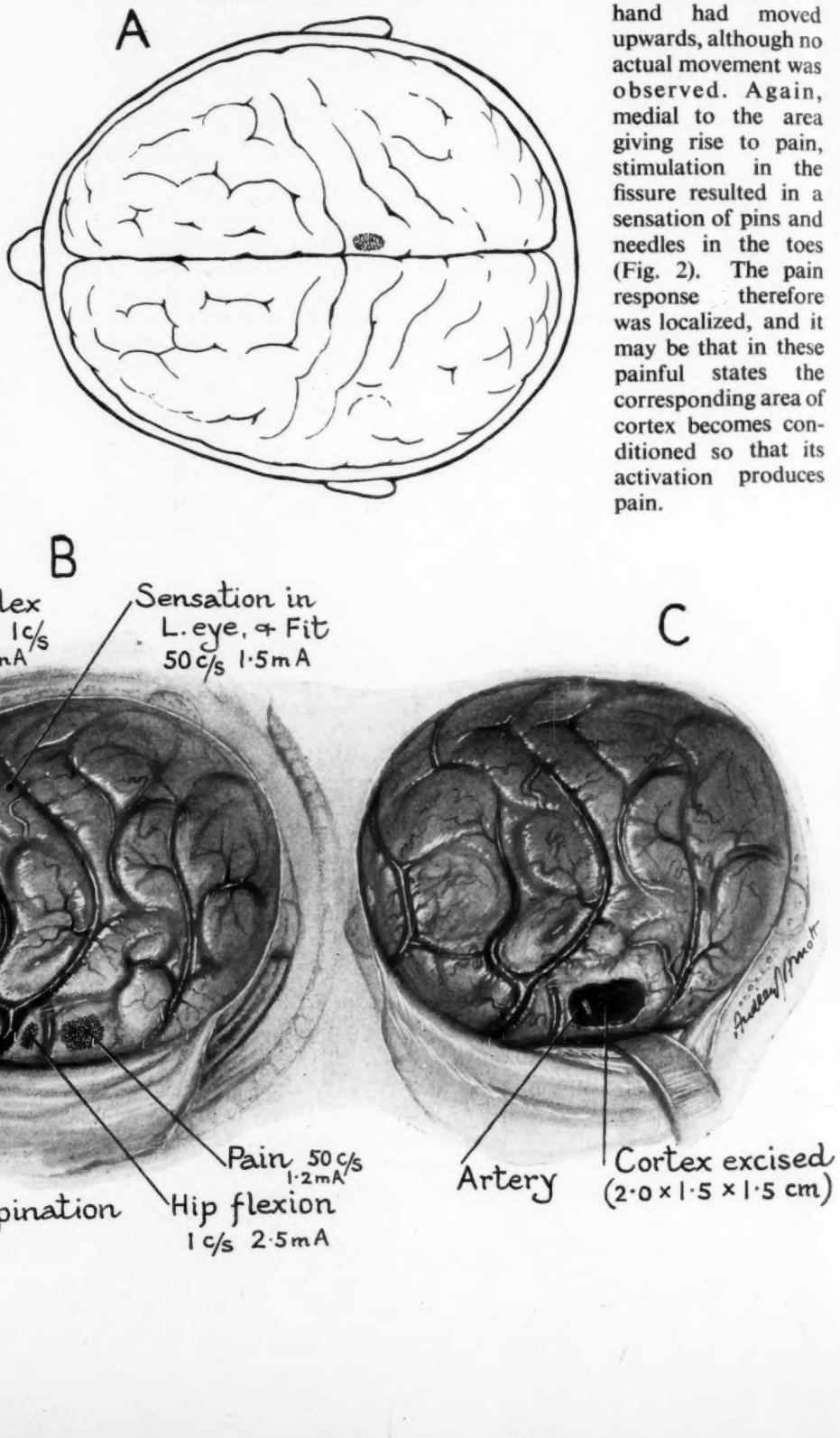
Results of Stimulation

The operations were conducted under local analgesia. Monopolar stimulation was used. The stimulator gave negative square pulses of current, the strength, frequency, and duration of which could be independently controlled. The position of the motor cortex was first identified by stimulation and then the post-central gyrus was explored. With varying parameters, different thresholds of stimulation in the motor and sensory cortex were established. Thus in Case 3, using single shocks of strength 1·5 mA and duration 5·0 m.sec., flexion and adduction of the thumb with abduction of the index was produced over a wide area of the motor cortex (Fig. 1B). Stimulation nearer the midline within this area at the same strength produced flexion of the wrist and supination, still, however, with the basic thumb-index response. The remainder of the motor area was unresponsive to these shocks. It was not possible to produce leg movement until the current was increased to 2·5 mA, and then in this case, still using single shocks, strong flexion of the hip was produced. These observations on the motor cortex were incomplete, since the primary concern was the sensory cortex and there was a limit to the time the patient would cooperate

accurately in responses to stimulation before he tired. Nevertheless, it does suggest that further observations on the unanaesthetized human cortex with varying parameters may yield results not dissimilar from those obtained in the baboon by Liddell and Phillips (1950).

With single shocks no response was obtained from the postcentral gyrus and the threshold seemed much higher than for the motor cortex. In all three cases a frequency of 50 c/s was required to produce a response. In Case 2, where it was possible to explore the sensory cortex more fully, pain in the phantom ankle was produced with a current of 50 c/s and 2 mA. Working over the surface of the postcentral gyrus in the hand area with the same current, no response was obtained, but stimulation of the posterior bank of the Rolandic fissure in this region resulted in a sensation as if the hand had moved upwards, although no actual movement was observed. Again, medial to the area giving rise to pain, stimulation in the fissure resulted in a sensation of pins and needles in the toes (Fig. 2). The pain response therefore was localized, and it may be that in these painful states the corresponding area of cortex becomes conditioned so that its activation produces pain.

FIG. 1.—Cortical excision and results of stimulation in Case 3.



Case Reports

Case 1 (H.N. 19059).—This soldier, aged 28 years, was injured on May 1, 1942, and sustained a penetrating gunshot wound in the right parietal region. He was taken prisoner and did not receive definitive treatment of his wound for five weeks. His residual disability consisted of an incomplete left lower quadrantic hemianopia and a little weakness of the left hand with minimal cortical sensory loss.

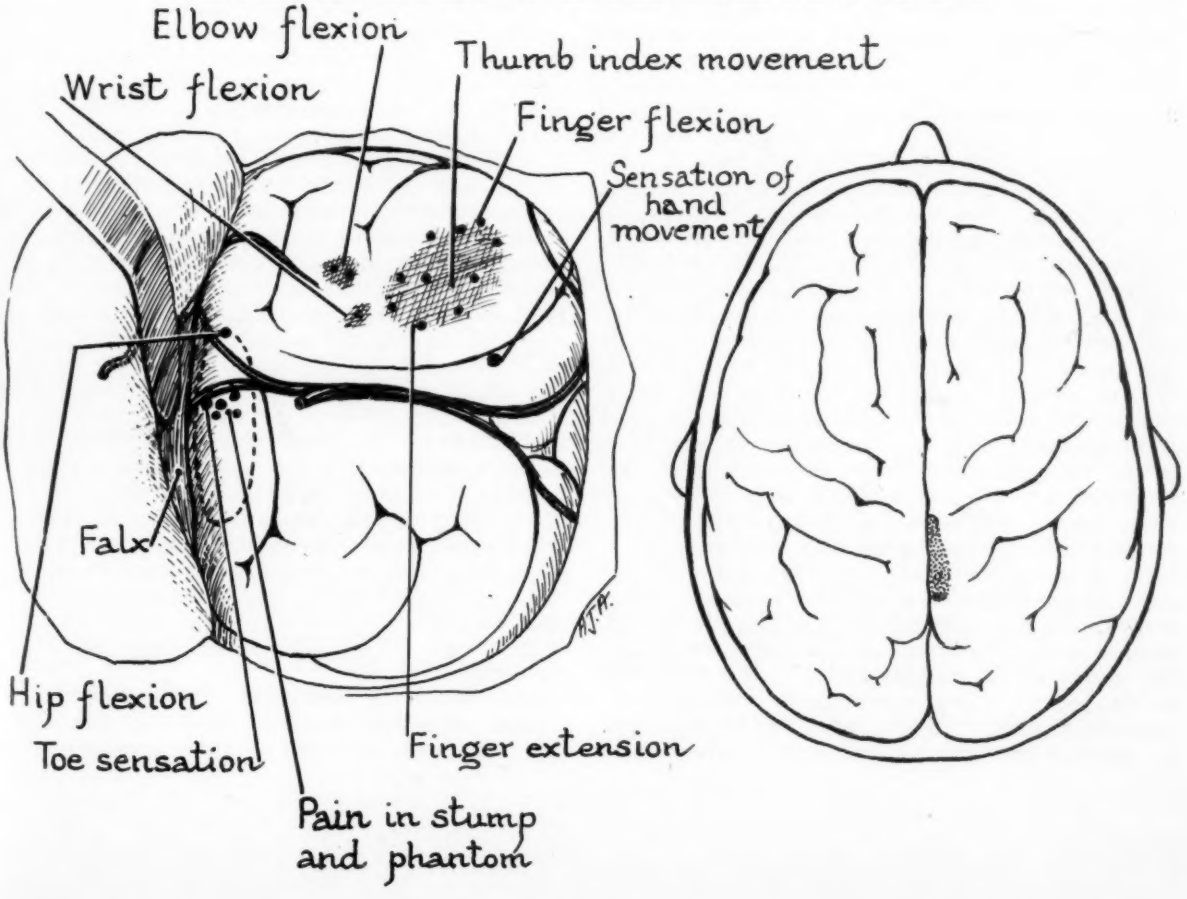
The patient had his first epileptic fit the day after his injury, the second five months later, and thereafter until his admission to the Military Hospital (Head Injuries), Oxford, in February, 1948, an attack at least every two months, sometimes two within a week. The attacks were characterized by a long, painful, sensory aura lasting five minutes before he lost consciousness. At the onset the left hand would be drawn into the side and the fingers begin to tingle; this sensation rapidly travelled up the outside of the arm to the shoulder, increasing in intensity and accompanied by a deep, gnawing pain in the wrist and hand. The forearm would feel as if it was being alternately blown up and deflated. By this time the patient said he would be confused but still able to lie down to await the attack and also to ask someone to place a prop between his teeth. The pain progressed to involve the face, the left eye, and finally the left eyebrow, at which stage he would lose consciousness. Associated with the later phases of the pre-ictal stage, objects in front of him rotated at increasing speed anticlockwise and were coloured red or yellow. He volunteered the information that the pain was torture, that he dreaded it more than the actual fit, and had even contemplated asking to have his arm amputated. The convulsion was generalized and was often followed by a pronounced automatism lasting two hours or so.

Examination in February, 1948, revealed the residual hemisphere signs mentioned above and a right parietal bone defect. An air encephalogram showed dilatation of the right ventricle with a traction diverticulum towards the bone defect.

On February 25, 1948, under local analgesia, a right lateral flap was turned down. The dural scar, 7·5 × 2·5 cm., was separated from the ventricular cyst by only a few millimetres' thickness of glial scar, and in opening the dura the ventricular diverticulum was entered immediately. The dural scar was therefore excised. The anterior extremity of the diverticulum was just behind the post-central gyrus and its lower limit lay 1 cm. above the line of the Sylvian fissure. The walls of the diverticulum were perfectly smooth except at one place in the anterior wall where in the depths was a small piece of greyish, congested cortex, 1·0 × 0·5 cm., across which ran a vein. Posteriorly the cyst communicated directly with the lateral ventricle through a small hole, through which the choroid plexus was drawn up. The rest of the exposed brain looked normal.

On stimulation no response was obtained from the cortex around the diverticulum but as soon as the piece of cortex in its anterior wall was stimulated the patient experienced tingling in the fingers of the left hand and

FIG. 2.—Results of stimulation in Case 2. The dotted line indicates the area of cortex excised.



pain in the hand exactly reproducing the onset of one of his attacks. From the lower part of this area, tingling in the cheek was produced. These responses were elicited on four successive occasions. Going well forward on to the normal cortex, stimulation resulted in movement of the left eye and a generalized epileptic fit. The abnormal piece of cortex was now excised to a depth of 2 mm., at which level the white matter lining the cyst wall was encountered.

Post-operatively there was no increase in weakness of the left hand but there was an increased sensory deficit, with complete astereognosis and some impairment of joint position sense. On the second post-operative day the patient had three fits. The aura in these was similar to those experienced before the operation but without the severe, gnawing pain.

When seen in January, 1952, four years after the operation, the patient was at work and said he had only had one fit since leaving hospital, in December, 1949. The fingers began to tingle in the same way as before but the aura was much shorter and unaccompanied by pain. He said that the sensation in the left hand had improved steadily for one year after leaving hospital. On examination, he was found to have complete recovery of position sense but stereognosis was still impaired and two-point discrimination was not quite as well appreciated in the left hand as in the right.

Case 2 (H.N. 22566).—This patient, a pensioner aged 66 years, had a left thigh amputation performed in 1916 after a torpedo explosion while on active service. From the outset he had a phantom limb but the only pain he experienced was a jerking in the ankle and heel about once or twice a week, sensations which were never incapacitating and did not interfere with his work as a boot repairer. This state of affairs continued until 1941 when he noticed that these sensations were becoming more frequent and distinctly painful. The stage was soon reached when the pain was interfering with his sleep. The pain was confined entirely to the phantom foot and described as a tearing pain around the heel and inside of the ankle, as though someone were trying to pull the ankle off. The pain also radiated into the toes. He had not experienced shortening of the phantom and when he stood up he felt the knee extended and the ankle dorsiflexed with the heel on the ground. Over the seven years up to the time of his admission in March, 1951, he had had numerous local operations and injections, including spinal analgesia, in an attempt to relieve the pain, without even temporary relief. He never had an undisturbed night's sleep and was on heavy barbiturate sedation. In 1950 a carcinoma of the rectum was discovered and treated by excision.

On admission the patient was in severe pain but co-operative and there did not appear to be any functional overlay. He looked much older than his years and was arterio-sclerotic, but despite his age and general health the severity of his pain demanded further treatment. In view of the failure of peripheral operations and analgesia, ablation of the sensory leg area was proposed. At operation on March 15, 1951, under local analgesia, the motor cortex was identified and movements obtained from the hand, elbow, and finally the stump. Stimulation of the post-central gyrus near the vertex just against the falx immediately produced his pain, and this observation was repeated several times. This response was obtained over an area measuring 1 cm. in diameter. This area was excised but it had no effect on the pain. Stimulation deep in the anterior cut edge, that is on the posterior bank of the Rolandic sulcus, still produced pain. The excision was gradually extended until an area of sensory cortex, $3{\cdot}0 \times 1{\cdot}0 \times 1{\cdot}0$ cm., was removed. Medially the excision extended down the medial side of the hemisphere for 1 cm. (Fig. 2). At this stage the patient was not quite free of pain but was considerably improved and it was decided therefore to terminate the operation.

Immediately after the operation the patient still had some pain in the phantom on direct questioning but no longer complained of it spontaneously and slept at night without sedatives. Neurologically there was no weakness in the stump or sensory impairment. The residual pain died away in the early post-operative weeks and the patient returned home. There for nearly six months he was completely free from pain, slept well, and got about on his artificial leg. He still had his phantom limb and toward the end of this time noted some return of pain. He was readmitted to hospital at the end of September, 1951, for review. Under observation it was obvious that there had been considerable improvement; he looked well, slept well, and such pain as he had was controlled with aspirin.

Case 3 (H.N. 25642).—This pensioner, aged 58 years, sustained a gunshot wound of the left leg in 1919; two years later a mid-thigh amputation was performed for non-union of the fractured femur. Thereafter he was perfectly well for 27 years and had no phantom. Then in 1946, for no apparent reason, pain began in the stump. It was localized to an area on the outside of the stump and the pain varied from a surface prickling sensation, of itself sufficient to keep him awake at night, to a severe, gnawing and gripping pain in the stump. At first intermittent, it had gradually become more persistent until at the time of his admission in September, 1951, the pain had been present without respite for seven months and the patient was beginning to feel desperate about the situation. He was an excellent type of man, who, despite his pain, had continued at his work as a ticket collector on the railway. Over the last five years he had had numerous local operations on the stump, a cordotomy in January, 1950, and a spinal analgesic in October, 1950. The cordotomy had relieved him for three weeks but the spinal analgesic gave no relief at all. On examination, he was in good physical condition and the stump was sound and strong. There was hemihypoalgesia to pin-prick and temperature sense extending over the stump and up to the lower costal margin on the left side corresponding to the cordotomy.

At operation in November, 1951, the cortex was exposed under local analgesia through a right lateral flap. The motor cortex was defined by stimulation, and

then precisely posterior to the motor region from which stimulation had produced flexion of the stump, stimulation resulted in a severe gripping pain in the stump, according to the patient, the same for which he was seeking relief. This response was reproduced several times. The pain induced was followed by jactitation of the stump. An area of cortex about 1 cm. in djameter was excised without, however, influencing his pain. At the bottom of the cavity so produced was the grey matter of the posterior lip of the central sulcus, and on pinching a small vessel here with forceps, the pain was again produced. As this grey matter was sucked away the pain disappeared. The final excision measured 2·0 cm. in the sagittal plane, 1·5 cm. in the coronal plane, and was 1·5 cm. deep (Fig. 1c). It did not extend on to the medial side of the hemisphere, although this formed the medial wall of the cavity and the cortex here had been undercut by the excision.

Following operation the patient had some superficial tingling in the stump which died away after a few days. Five days after operation he awoke with a burning pain in the stump quite different from any pain he had had previously, and this was accompanied a few hours later by numbness in the ring finger of the left hand and slight clumsiness of the hand. All these symptoms cleared up within 17 hours. On the fifth day he had a brief attack of numbness in the left ring finger lasting 10 minutes. Thereafter there were no further incidents, and when discharged home five weeks after operation he had been completely relieved of his pre-operative pain although he was having a few aching pains over a small area of the stump which were insignificant by day but worried him at night. There had been no change in the motor or sensory state of the stump following the operation.

Comment

Whether removal of these small areas of sensory cortex will permanently relieve pain is still undecided. Some published reports on the results of this operation for phantom limb pain up to two years after operation (de Gutiérrez-Mahoney, 1944 ; Echols and Colclough, 1947 ; Stone, 1950) are encouraging, and although there are disappointments in trying to relieve this type of pain (Lhermitte and Puech,1946 ; de Gutiérrez-Mahoney, 1948), and more especially in other painful states (Horrax, 1946 ; Rowbotham, 1946), it would perhaps be surprising if this were not so. Only that part of the sensory representation which produces pain on electrical stimulation is removed by this operation, with, in some cases, a small area of cortex immediately adjacent. The strychninization experiments of Dusser de Barenne (1924), Penfield's observations on the human cortex, and Woolsey's work (1943, 1947) on the second sensory cortex suggest that the pre-central gyrus and cortex near the Island of Reil are also concerned in somatic sensory representation.

The attraction of such an operation is the possibility of relieving pain without producing any marked permanent motor or sensory deficit or personality change. The possible sequel is the production of epilepsy but so far there is no record of this complication. If further experience is favourable, the place of the operation in treatment will have to be considered in relation to alternative operations on the frontal lobes.

The results of stimulation in these three cases are in contrast with the observations of Penfield and others, and might appear at first sight to lend support to the contention that there is cortical representation of pain. However, it has to be remembered that these responses were obtained in patients experiencing severe spontaneous pain. All we may conclude is that in these patients spontaneous pain is associated with activation of the sensory cortex. It need not follow that normal conscious appreciation of painful peripheral stimuli concerns the sensory cortex.

Summary

Three cases are recorded in which partial resection of the post-central gyrus was undertaken for the relief of severe limb pain.

Observations are made on the electrical stimulation of the motor and sensory cortex of these patients. In each case stimulation of the appropriate area of the post-central gyrus reproduced the pain complained of by the patient, and relief followed the removal of this area of cortex.

The significance of these findings is discussed.

Our thanks are due to Dr. W. Ritchie Russell for his encouragement in this work, and for reporting these patients for treatment ; to Miss Arnott for the illustrations, and to Miss F. M. Taylor for her assistance.

These patients were treated in the Military Hospital (Head Injuries), Oxford. We wish to thank Major-General A. G. Harsant, Director of Surgery and Consulting Surgeon to the Army, for permission to publish.

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MICTURITION REFLEXES IN MAN

BY

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Barrington (1921), during his investigation of " the reflexes composing reflex micturition " in the cat, found that " active contraction of the bladder " was caused either by distending the bladder " or by slightly moving the catheter in and out in the direction of the urethra ". He found that this reflex contraction of the bladder could be evoked by " withdrawing the catheter a fraction of a centimetre and then pushing it back to its original position ", or " by running water through the urethra ". Although the rise of bladder pressure produced in this way was not quite as high as that produced by distension, on one occasion the pressure rose to thirteen and a half times its original value. " In many cases ", Barrington wrote, " it was quite enough to start reflex micturition, the bladder contents being passed at the side of the catheter ".

This stimulation of the urethra causing contraction of the bladder constitutes Barrington's second and seventh reflexes of micturition. The difference between the two reflexes is that in the second the afferent pathway is in the pudic nerves and the efferent pathway in the pelvic nerves, while in the seventh reflex both afferent and efferent pathways are in the pelvic nerves (Barrington, 1941).

Langworthy, Kolb, and Lewis (1940) confirmed the presence of these reflexes in the cat.

From this experimental work it has been concluded that this reflex contraction of the bladder plays an essential part in normal micturition, keeping the bladder contracting as long as urine flows through the urethra. And the presence of residual urine in animals with lesions of the spinal cord has been attributed in part to interruption of these reflexes by the division of the pathways concerned.

During the course of a recent investigation of the effects of lesions of the nervous system on micturition in man, it was noted that the movement of catheters or cystoscopes in and out of the urethra caused no obvious changes in pressure and no contraction of the detrusor. As this was contrary to expectation, in view of Barrington's work, it was decided to subject this observation to more careful and detailed analysis.

The following procedure was adopted in 16 subjects. In all subjects a cystoscope was passed and connected to a water manometer; in the majority on another occasion a catheter was passed into the bladder and connected to the manometer. The bladder was then filled till the subject had a desire to micturate, at which time detrusor contractions occurred spontaneously or could be easily evoked by increasing intra-abdominal pressure or by adding a little more fluid. When this activity had subsided, the catheter or the cystoscope was pushed in and out along the urethra. During catheterization the pressure was recorded, and during cystoscopy the bladder was examined for detrusor activity.

The subjects investigated in these ways consisted of six women and 10 men, who were attending hospital on account of the following disorders: one had a cerebral thrombosis, three had each a single papilloma of the bladder, one had a small nodule of a carcinoma of the bladder, one had previously had a stricture of the urethra, one attended on account of phosphaturia, and the other nine had carcinomata not involving the urinary tract.

In no instance did any of these procedures outlined above cause any rise in vesical pressure or evidence of detrusor contractions.

The observations made on one of these patients, who had previously had a stricture of the urethra, deserve further attention. This subject had a most urgent desire to micturate when the bladder contained a relatively small amount of fluid, and the bladder so often contracted spontaneously that it was difficult to find a period of quiescence of sufficient duration to carry out the stimulation of the urethra. Nevertheless, when, during a period of quiescence, the urethra was stimulated by sliding the cystoscope in and out, no detrusor activity was induced.

Although Barrington evoked this reflex contraction in the decerebrate cat by moving a smooth foreign body along the urethra, the normal stimulus for this reflex might be thought to be an increase in tension in or a dilatation of the urethra. This stretching of the urethra was reproduced in two normal women and one normal man by means of a Foley catheter. The catheter was passed until the tip was in the bladder; thus the bladder pressure could be recorded. The whole length of the urethra of the female subjects was then distended by blowing up the bag; in the man, that part of the urethra which is common to both sexes was similarly distended. No evidence of bladder contraction was obtained by suddenly dilating the urethra in this manner.

Barrington evoked these two reflexes also by running water through the urethra. This experiment was repeated as nearly as possible on human males with intact nervous systems. Four elderly men were examined, who had had suprapubic cystostomies performed, owing to the obstruction associated with enlargement of the prostate. In none of these cases was the detrusor atonic. This was shown by recording the pressure from the suprapubic tube; when the patient strained to micturate or when the bladder was stretched by filling, the detrusor contracted, raising the pressure to 60 or 110 cm. of water. (The rise in bladder pressure transmitted passively from the rise in intra-abdominal pressure is of the order of 10 cm., and comes on immediately, whereas the rise in pressure due to the reflex evoked by increasing intra-abdominal pressure comes on after a latent period, often, indeed, as the intra-abdominal pressure subsides.) In these four subjects the pressure was recorded from the suprapubic tube, while the urethra was stimulated to evoke the reflex. A narrow catheter was introduced into the urethra after the bladder has been distended with fluid; no change in bladder pressure occurred as the catheter was passed along the urethra into the bladder. It was then withdrawn; no change in bladder pressure occurred, as this smooth foreign body was dragged through the sphincters along the urethra. The catheter was then re-introduced into the bladder. Micturition around the catheter was then induced by suddenly adding fluid at a pressure of 40 cm. through the catheter into the already full bladder. After 15 to 20 ml. of fluid had been passed around the catheter the bladder ceased to contract, and the spontaneous flow down the urethra stopped. Immediately the flow of fluid stopped, the catheter was again slowly withdrawn down the urethra, and as it was being withdrawn, fluid was made to flow out of it, irrigating the urethra. But the continuous stimulation of the urethra by the stream of fluid flowing down it did not induce the bladder to contract again, and no further micturition took place.

From the investigations reported here, no evidence has been found for the existence in conscious man, with an intact central and peripheral nervous system, of the second and seventh reflexes which Barrington found in the decerebrate cat.

If these reflexes were active in man, cystoscopy could be carried out only with difficulty, for the detrusor would contract whenever the cystoscope was moved along the urethra. Further, one might have expected micturition to take place during catheterization. This rarely occurs in man. Jacobson (1945, 1952) who catheterized conscious, unanaesthetized, female dogs, did not find micturition occurring during catheterization of these animals.

The question why the bladder continues, as it usually does, to discharge its contents after its pressure has fallen to a level insufficient to cause contraction, would now seem to remain unanswered, for it has usually been assumed that Barrington's second and seventh reflexes supplied the answer.

Summary

The reflex contraction of the bladder evoked by moving a smooth foreign body along the urethra or by irrigating the urethra with fluid, as described by Barrington in decerebrate cats, and named by him the second and seventh component reflexes of micturition, was sought for in man. No evidence has been found of its existence.

I should like to thank Mr. Philip Ryan for his help in this investigation, and Mr. Norman Matheson and Mr. Harland Rees for being so kind as to put their cases at my disposal, and Mr. F. J. F. Barrington and Dr. E. A. Carmichael for their interest and critical advice.

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THERMAL SENSATION IN THE BLADDER

BY

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It has been pointed out in an earlier paper by Nathan and Smith (1951) that " it is not yet definitely known whether the bladder mucosa is sensitive to thermal stimuli ". As a review of the literature has shown that there is no generally accepted opinion on the presence or absence of such sensation, the present investigation was undertaken.

Guyon (1887) stated that one could feel in the bladder definitely whether liquids were hot or cold. Von Frankl-Hochwart and Zuckerkandl (1906) wrote that " the delicate sensitivity of the bladder to thermal stimuli is well known ". Zimmermann (1909) investigated the sensation by means of passing a urethral catheter on himself and running through it into the bladder fluids at temperatures of 0° C. and 50° C.; he found that temperature was appreciated in the distal 2 to 3 cm. of the male urethra, but nowhere more proximally in the urethra, nor in the bladder. Müller (1919) reported that one of his colleagues, who investigated thermal sensation on his own bladder, found no sensation evoked by temperatures as different as 0° C. and 45° C. Waltz (1922), using a double-walled, glass urethral catheter, to avoid thermally stimulating the urethra, came to the conclusion that the bladder is insensitive to thermal stimulation. He also applied menthol to the mucosa ; this caused no sensation, whereas, when it is applied to the skin, it stimulates cold spots, causing a sensation of cold. Moore (1924) investigated bladder sensation by passing " knobbed applicators " along the urethra ; the sensitivity to thermal stimuli was examined by passing through a cystoscope such an instrument, consisting in this case of a glass tip 2 cm. by 4 mm. on a steel wire, which had previously been immersed in water at 60° C. and 15° C. He concluded that " heat was perceptible in every instance in the normal bladders . . . Cold was not as readily detected as heat ". Dees and Langworthy (1935) expressed the opinion that there is " a crude recognition of temperature in the mucosa " ; and Langworthy, Kolb, and Lewis (1940) held the view that the bladder mucosa is " slightly responsive to heat, cold, and touch ". McLellan (1939) stated : " Thermal sensory nerve endings are present and the patient is generally aware of heat or cold and variations in the temperature. . . . The bladder differs from other abdominal viscera in that it has the presence of thermal and tactile sensory endings ". McLellan and Goodell (1943) later investigated thermal sensation by permitting fluid to pass into the bladder through a urethral catheter ; they found that fluid at 45° C. was felt to be hot, and fluid at 0° C. " very cool ". Band (1950) stated : " The bladder wall can distinguish between the hot and cold lotion employed for lavage ".

As nearly all investigators passed liquids at various temperatures into the bladder through the urethra, it is possible that the disagreement concerning the observations may have arisen from neglecting the fact that the urethra is sensitive to thermal stimuli. As stimuli applied to the bladder are usually referred to the urethra, it is easy to see that the subjects being investigated might have been able to tell the temperature of the liquids, without being able to tell whether they experienced the sensation in the bladder or the urethra. This criticism applies least to Moore and Waltz, but they reported opposite findings.

Material and Methods

A method of dealing with this problem was required that permitted the direct application of liquids at various temperatures to the bladder, avoiding thermal stimulation of the urethra. Accordingly, patients having suprapubic cystostomies were investigated. It was, incidentally, difficult to find enough suitable patients for such an investigation. For the main source of such material, patients having prostatectomy, is not very satisfactory ; the reasons for this are that this operation is nowadays usually performed in one stage, and that such patients are usually old and

not necessarily vigilant and scrupulous observers. Patients with disorders of the nervous system causing disorders of micturition cannot be used for an investigation of sensation. Again, many patients with suprapubic cystostomies cannot be used, as the stoma leaks, permitting the fluid to reach tissues known to be sensitive to thermal stimulation. The most suitable are those who have had the cystostomy made about a week previously, as the stitches are still in the abdominal wall, preventing leakage, and cystitis is minimal.

Fifteen patients were examined. The bladder was emptied, and then fluid of known temperatures was allowed to flow into it through the suprapubic tube. During the next minute or two, the patient was asked to say what he felt, and if he made no comment on thermal sensation, direct questions were put to him. The bladder was emptied, and refilled with fluid at another temperature. The temperature of the first fluid to be run in was either in the neighbourhood of 45° C., or of 15° C.; the succeeding irrigation was at the opposite end of the scale, so that the stimuli applied were maximally contrasted. The limits of the temperatures used were 49°–15° C.; about four different temperatures were applied to each patient. The patient was encouraged to compare each irrigation with the previous one.

Results

None of the patients gave any satisfactory evidence of possessing thermal sensation in the bladder.

Typical comments of one patient were as follows : 21° C.: slight pricking, no thermal sensation ; 42° C.: slight pricking, no thermal sensation ; 21° C.: no thermal sensation ; then (after he had been persuaded to try and feel some thermal sensation) " probably warmer than the last one ".

One of the 15 patients, who had previously had the prostate removed, experienced a sensation only when a hot fluid was employed : fluids at 18° C. or 37°C. gave rise to no sensation, but fluids at 45° C. and 48° C. were both felt as " definitely warm " ; this sensation was not immediate but delayed.

Three other cases, not included in the above 15, are relevant. One patient, with carcinoma of the cervix, having normal bladder function and no involvement of the bladder by growth, had no thermal sensation in the bladder or urethra. When fluid was passed into the bladder per urethram she could not tell its temperature. Thus fluids at 44° C. and 16° C. were called warm, while fluids at 25° C. and 28°C. caused no sensation. Another patient, suffering from motor neuron disease, had very poor urethral thermal sensation ; his bladder was filled through a urethral catheter. He experienced no sensation with temperatures of 37° C. or 24° C.; 44° C. felt warm in the penis, but " caused no sensation inside ". One other patient, attending hospital on account of a urethral caruncle, stated, when fluid at 25° C. was run into her bladder through a urethral catheter, that it felt cold in the urethra and warm in the bladder.

Conclusion

The human bladder is insensitive to thermal stimuli.

I should like to thank Mr. Norman Matheson, Mr. Harland Rees, and Mr. W. L. F. Utley for allowing me to investigate cases under their care ; and Dr. E. A. Carmichael for his useful advice.

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TWO CASES OF ASPERGILLUS INFECTION OF THE CENTRAL NERVOUS SYSTEM

BY

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Fungus infections of the nervous system are admittedly rare and the report of additional cases can be justified only if they demonstrate new facts. We believe this to be true of the following two cases. They present certain clinical features not described previously in association with aspergillosis and also exhibit an unusual combination of pathological changes which aid in the interpretation of the pathology of other types of chronic inflammatory disease of the central nervous system.

Case Reports

Case 1.—The patient, a 23-year-old man, was admitted to the Tokyo Army Hospital on February 18, 1951, because of increasing headache, double vision, and stiffness of the neck. The symptoms had begun in October, 1949, and the first complaint was severe aching pain over the maxillary and frontal sinuses. These pains persisted intermittently until June, 1950, and were followed by a constant burning pain in the right occipital region. The latter was most severe in the morning and in the late evening. There was no accompanying nausea or vomiting and change of posture did not influence the pain. The pain ceased about October, 1950.

In November, 1950, while in Korea, the patient awoke one morning with stiffness and aching in the left shoulder and left side of the neck. The ache was relieved by inclining the head to the left. Weakness of the left shoulder and upper arm was also noticed about this time and these symptoms progressed until January, 1951. The aching pain then ceased but weakness and also a stiffness of the left shoulder and upper arm remained. Diplopia was experienced for the first time on February 4, 1951. From the beginning it was worse on lateral gaze, and it gradually increased in severity. At times there was an associated dizziness but never a true vertigo. Unsteadiness of gait was also noted about this time and became progressively worse. On February 10, 1951, the patient began to suffer with severe occipital and bitemporal headaches, and boring pains behind the eyes. After the headache had continued for eight days he was admitted to the hospital. Twenty pounds in weight had been lost during the course of the illness.

A review of the past history contributed relatively little of value. The patient was born and had lived most of his life in Mississippi. There had been no serious past illnesses. In the year and a half before admission he had been stationed in China, Guam, Okinawa, Japan, and Korea. The family history was not contributory.

On admission the patient came under the care of one of us (P.R.D.). It was observed that he was rather thin but he did not appear to be particularly ill. Temperature, pulse, and respirations were normal and blood pressure was 120/80. The skin was covered with numerous pigmented moles and a large café-au-lait spot was noted in the right axilla. The superficial lymph nodes were not palpable. There were no abnormalities of the ears, nose, throat, and bony sinuses, and the heart, lungs, and abdomen were not remarkable.

The patient was alert, rational, and cooperative. There was papilloedema, estimated at two to three diopters. There were retinal haemorrhages bilaterally. The visual fields were of normal configuration except for an enlarged blind spot on the left ; visual acuity was within normal limits. The pupils were round, regular and equal in size, and reacted normally. There was bilateral lateral rectus weakness which was more marked on the left. No nystagmus was elicited. All other cranial nerves functioned normally. All of the muscles of the left shoulder girdle and the flexors of the left arm were weak and atrophic and numerous fascicular twitchings were seen in them. The left biceps reflex was definitely diminished and the left supinator reflex questionably so ; the triceps reflexes were equal and active. The left knee jerk was slightly more active than the right and the ankle jerks were equal. The plantar reflexes were flexor. There was no defect in sensation. Movements of the limbs were well coordinated ; the gait was normal and Romberg's sign was absent.

Laboratory Data.—The white blood cells numbered 8,300 with a normal differential count. The sedimentation rate was 5 mm. at the end of one hour, and the haematocrit value was 52%. Serological tests for syphilis were negative. Urine analysis was within normal limits. Radiographs of the chest did not reveal any remarkable findings. A lumbar puncture was not performed on admission because of the severe papilloedema and headache.

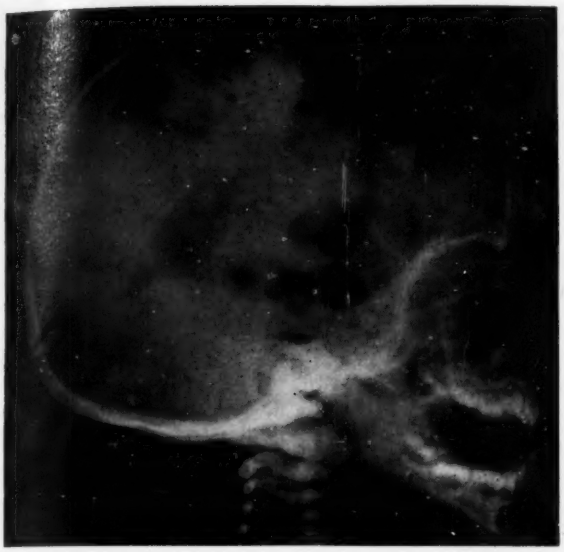


FIG. 1.—Pneumoencephalograms.

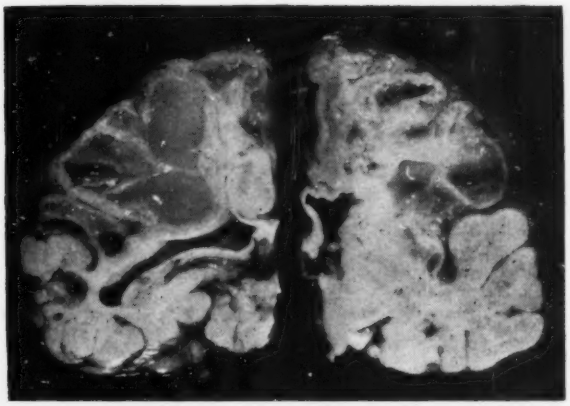
A. Case 2. There is incomplete filling of ventricles and moderate amounts of air over the surface of the brain. Wisps of calcium can be seen behind the lateral ventricle.

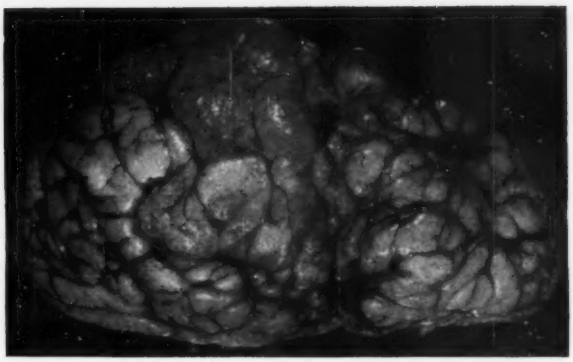
B. Case 1. The lateral ventricles are moderately dilated.

FIG. 2.—Necropsy material from Case 2.

A. Coronal section through the parietal lobes. Note the extensive destruction of brain tissue and the numerous cavities filled with a gelatinous material.

B. The same distended cavities in the fronto-parietal region as seen from the surface of the hemisphere.





Course.—The clinical findings remained the same except for the appearance of a mild antero-posterior rhythmical titubation of the head. A ventriculogram was performed on February 27, 1951, and a symmetrical enlargement of the lateral and the third ventricles and the upper portion of the aqueduct of Sylvius was demonstrated (Fig. 1B). The ventricular fluid was blood-tinged (traumatic) and contained 41 mg. of protein per 100 ml. The same day a suboccipital craniectomy was performed by Lt.-Col. A. M. Meirowsky. The dura was tense and the cisterna magna contained a small amount of normal-appearing fluid. The arachnoidal membrane over the dorsal surface of the lower medulla and upper cervical spinal cord was thin and transparent. A good view of the fourth ventricle was obtained and a catheter could be passed easily from the fourth ventricle through the aqueduct. A smooth, lobulated, pearly-yellow mass was seen lying ventro-lateral to the lower medulla and upper cervical spinal cord. Two large vessels were seen to enter the mass. The mass was firm and adherent to the medulla ; it was thought to be a benign neoplasm. It was considered to be inoperable because of its ventral location. Biopsies taken at this time and at a subsequent operation two days later disclosed a chronic granulomatous inflammation with marked fibrosis, round cell infiltration, and foreign-body giant cells. In the second biopsy the hyphae of a fungus were seen in a necrotic focus. The microscopic appearance of these hyphae suggested ustilagomycosis (Moore, Russell, and Sachs, 1946) but cultures taken at the time of the operation remained sterile.

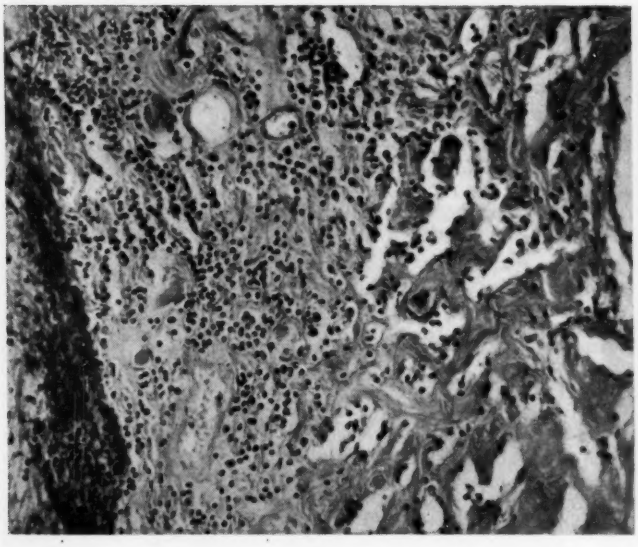
Following operation the patient showed no significant

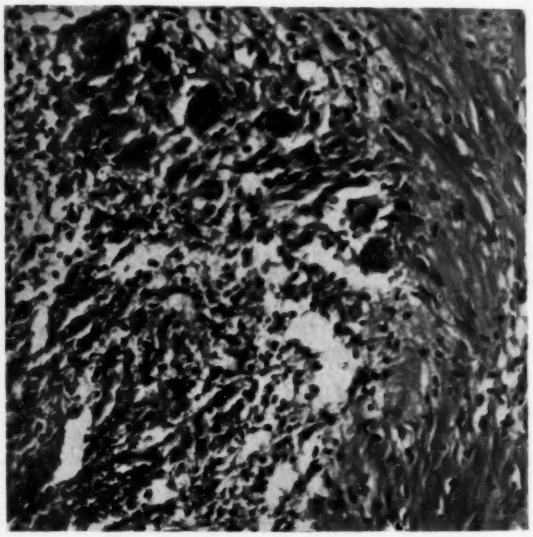
FIG. 3.—Photomicrographs of sections from Case 1 stained with haematoxylin and eosin.

A. Coronal section through the medulla at the level of the inferior olivary nuclei showing the mass of fibrous and granulomatous tissue lying ventral to the pyramids.

B. The meningeal mass at the level of the cervical cord. There is a small granuloma containing inflammatory cells (some degenerating), histiocytes, and multinucleated giant cells. Note the dense fibrous capsule.

C. Same level as B but showing a rather sparse infiltration of inflammatory cells and an abundance of dense collagenous connective tissue.





alteration in his vital signs. The diplopia persisted and ocular movements were now greatly impaired ; he was, in fact, unable to move either eye horizontally and on attempting extreme left gaze only a few slight unsustained adduction movements of the right eye beyond the midline were noted. Vertical movements were unaffected. The pupils were equal and reacted normally. There was gradual regression of the papilloedema. Three days after the operation the spinal fluid contained 40,000 erythrocytes and 351 leucocytes per 100 c. mm.; the protein was 110 mg. per 100 ml. Cultures were again negative.

On the evening of March 16, 1951, severe generalized headache and pain in the neck returned for the first time since operation. The patient became lethargic and slow to respond. The left knee and ankle jerks were hyperactive, the abdominal reflexes were absent on the left, and the left plantar reflex was extensor. Shortly thereafter he developed retention of urine which required constant drainage of the bladder.

On March 17, 1951, a ventricular puncture was performed, and the intraventricular pressure was found to be normal. The ventricular fluid contained 55 mg. of protein and 55 mg. of sugar per 100 ml. The lumbar puncture was repeated and an almost complete block in cerebrospinal fluid dynamics was found. The lethargy continued for several days and an intermittent fever up to 101°F. was recorded. When examined on March 25, 1951, the patient was disorientated. The papilloedema had subsided. A left Horner's syndrome was noted for the first time. The other findings were unchanged. The patient died at Tripler Army Hospital, Hawaii, while on his way to the United States.

Post-mortem Examination.—The necropsy was performed approximately 30 hours after death.* A moderate degree of emaciation was evident at this time. The cranial operative incisions were well healed. A small decubitus ulcer was present over the posterior aspect of the right iliac crest. There were no significant gross anatomical findings outside the central nervous system ; in particular, the lungs, heart, liver, spleen, and the gastro-intestinal tract were not remarkable either by gross or microscopic examination.

The dura was adherent to the galea aponeurotica in the region of the operative defect in each parietal bone and in the occipital region. At the base of the brain there were a few adhesions between the dura and arachnoid. The tentorium was also adherent to the upper surface of the cerebellum. The cerebral hemispheres were symmetrical and of normal appearance from the external aspect. The leptomeninges and vessels on the supero-lateral surfaces of the brain were normal. At the base of the brain on the left side the trigeminal, facial, and auditory nerves were enveloped by a mass that was situated anterior to the brain-stem. It had produced a pressure defect to a depth of 0·7 cm. on the surface of the brain-stem over an area that measured 2·5 × 1·5 cm. A series of sections through the cerebral hemispheres revealed moderate dilatation of the lateral and third ventricles and the aqueduct of Sylvius. The basal ganglia and the choroid plexuses appeared normal. The meningeal mass was firm and fibrotic. When the brain-stem was sectioned the asymmetry of the basilar pons, the upper medulla, and the left quadrangular lobe of the cerebellum was more clearly seen. Below the level of the medulla the mass thinned out to such a degree that it was no longer visible. The spinal leptomeninges were slightly opaque and thickened but no lesions were noted in the substance of the cord, and the spinal roots were of average size.

Sections of the spinal cord, medulla, pons, midbrain, cerebellum, and the cerebral cortex were prepared for microscopic examination by staining with haematoxylin and eosin.

Over the ventral surface of the upper cervical spinal cord the thickened leptomeninges formed a dense mass composed of several layers of collagenous connective

*Necropsy was performed by Lt. Donald G. McLeod who very kindly made available to us the gross findings and microscopic sections.

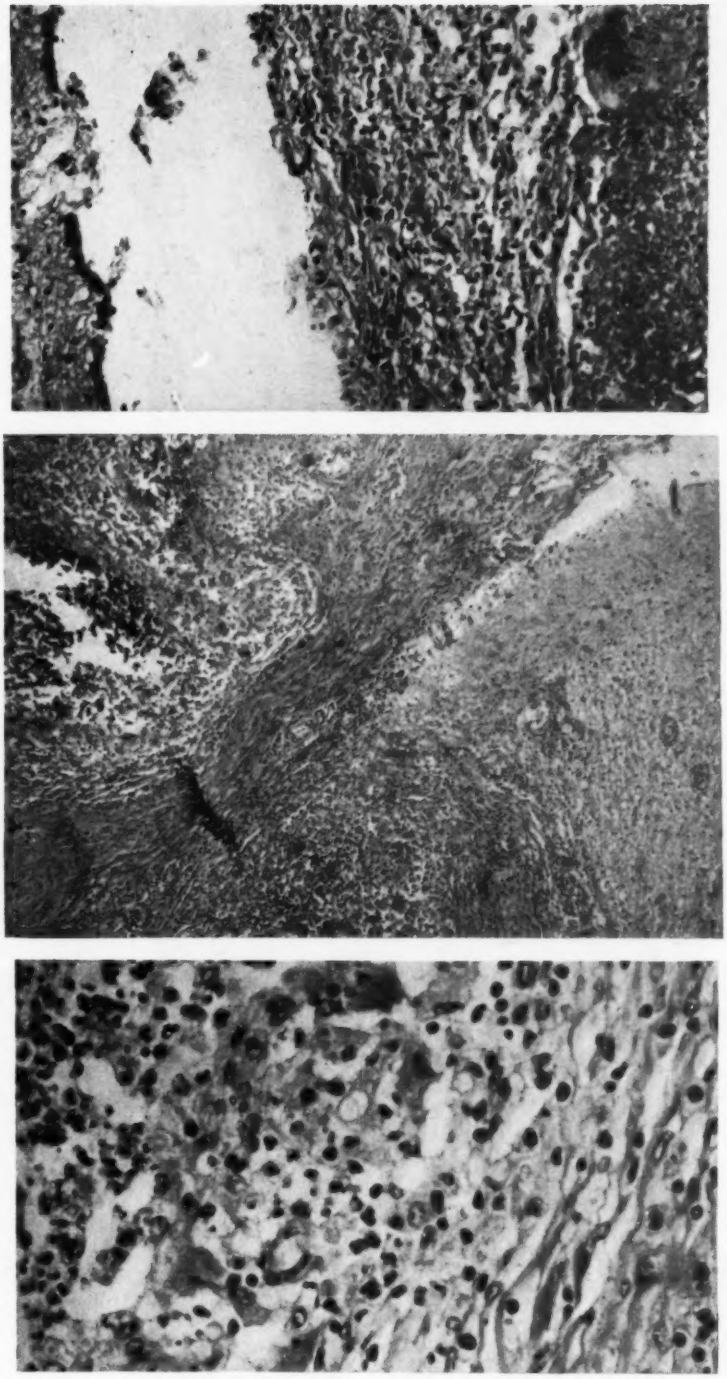
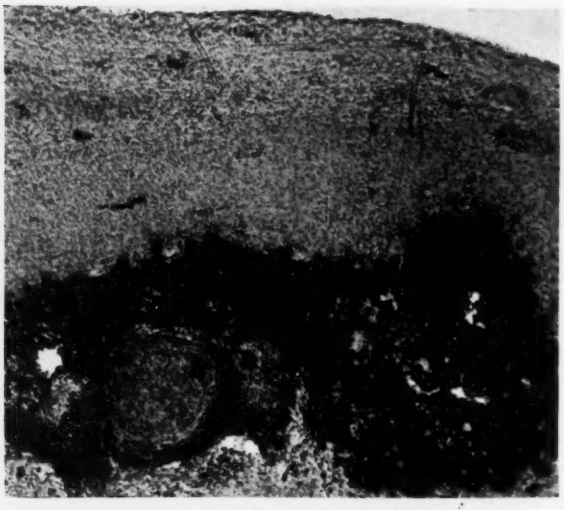


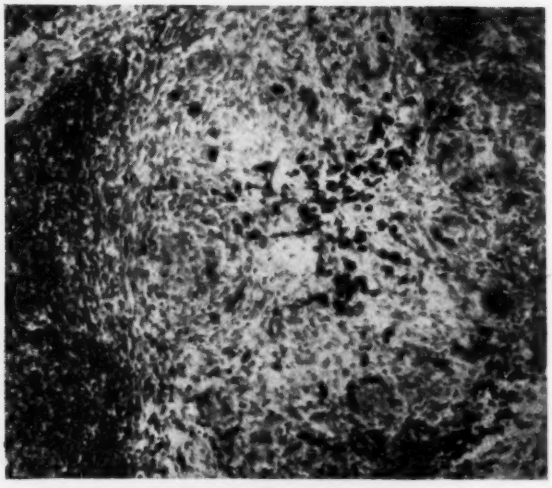
FIG. 4.—Photomicrograph of section from Case 1 stained with haematoxylin and eosin.

A. The ependymal lining of the floor of the fourth ventricle is shown on the left. The tissue on the right is a mass of astrocytes, histiocytes, and fibroblasts and partially fills the fourth ventricle and is attached to its floor in several places. One giant cell is seen in the right upper corner.

B. Section at the junction of pons and midbrain to show a granulomatous mass invading the subpial tissues.

C. Same level as B. The fragmented nuclei on the left represent a small abscess. Fibroblasts, lymphocytes, plasma cells, and histiocytes are seen on the right and in the centre.





tissue. Small abscesses and granulomas were embedded within this membrane. In the centre of the abscesses there was necrosis and only the debris of leucocytes and other cells remained. These abscesses were encapsulated by fibroblasts; also occasional giant cells and numerous inflammatory cells were seen (Fig. 3B). Several granulomas were observed, in some of which there were foreign-body giant cells and epithelioid cells surrounded by a peripheral zone of lymphocytes and plasma cells. Fungi were not seen either in the abscesses or granulomas at this level. The nerve roots in the thickened leptomeninges were not damaged. Elsewhere in this membrane small blood vessels were dilated and diffuse and focal infiltration of inflammatory cells were observed (Fig. 3C). There were no changes in the substance of the spinal cord other than a few mononuclear cells around the central canal.

Sections through the junction of the pons and medulla showed a similar dense granulomatous mass ventral to the pyramids (Fig. 3A). In addition to numerous small abscesses and granulomas several thrombosed and recanalized arteries were seen at this level. Branched, septate, highly refractile rods were seen in the centres of the abscesses (Fig. 6A). There were focal collections of microglia under the pia in the ventral portion of the medulla. The floor of the fourth ventricle was covered by a granulomatous mass which replaced the ependymal lining in some places and buried islands of ependymal cells in others (Fig. 4A). At one point the inflammatory process extended through the ependymal lining into the tegmentum of the medulla. There was hyperplasia of the endothelial and adventitial cells of numerous small vessels in the sub-ependymal zone, and the Virchow-Robin spaces of some of these vessels contained mononuclear cells. A diffuse microglial proliferation was seen in the dorsal tegmentum of the pons. Occasional hyphae were found in the granulomatous formations in the ependyma but there were none in the sub-ependymal layer. The ependymitis appeared to be fairly recent, especially in one side of the fourth ventricle where a mass of fibrin and leucocytes was found attached to the ependyma.

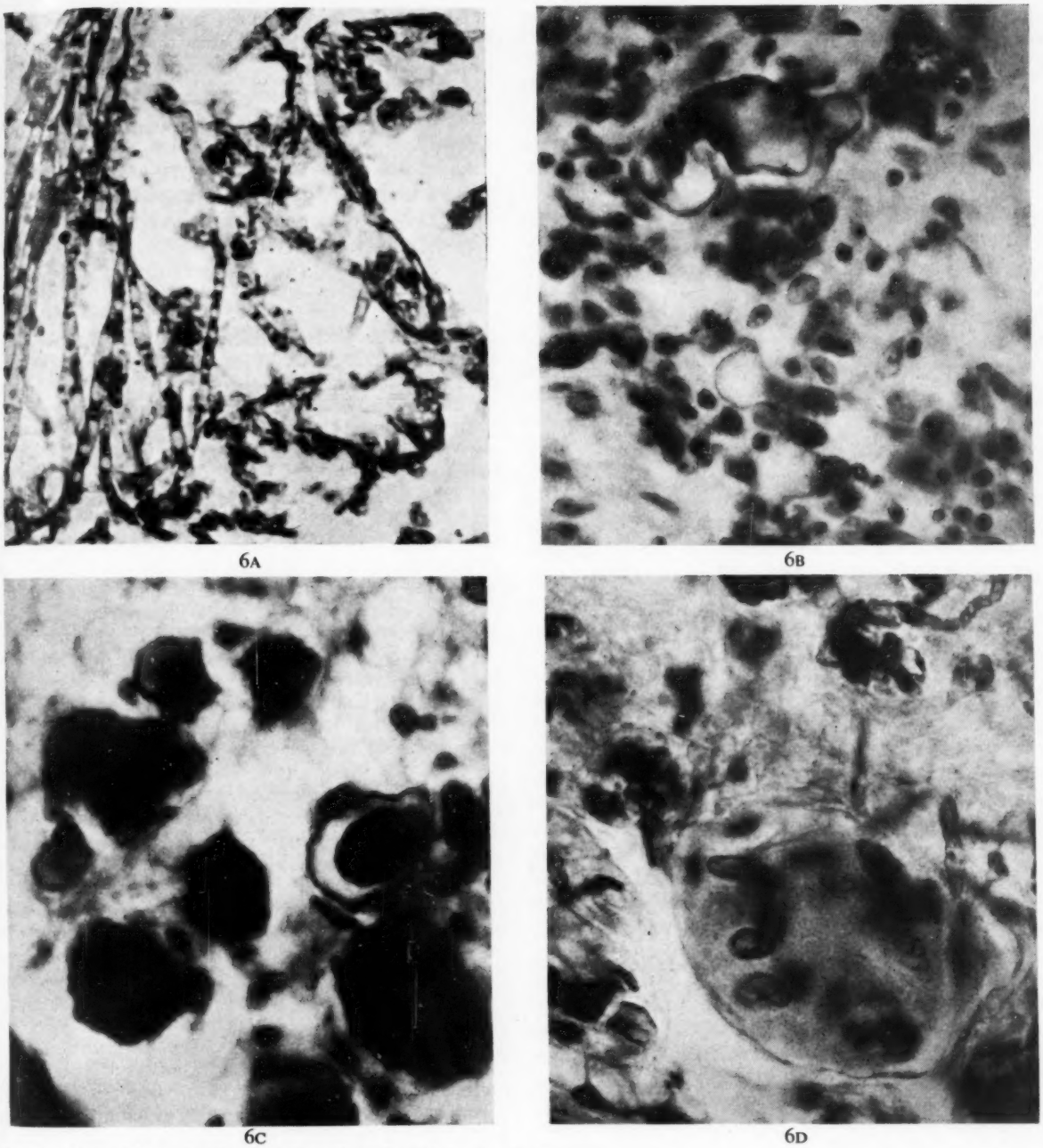
Sections through higher levels showed the fibrogranulomatous mass to have invaded the brain stem in two places. One such lesion, situated in the basis pontis at the junction of the pons and midbrain, is pictured in Fig. 4B. Here within the pons there was a small abscess walled off from the rest of the pons by a zone of collagenous connective tissue containing numerous lymphocytes, occasional plasma cells, polymorphonuclear

FIG. 5.—Photomicrographs of sections from Case 2 stained with cresyl violet.

A. Cerebral cortex: the black material is calcium and several small granulomas are visible. The nerve cells in the cortex are replaced by astrocytic glia.

B. Same level as A, demonstrating densely cellular granulomas with one large giant cell. Collections of fungi with Hülle cells can be seen in the centre of the granuloma on the right.

C. Note the extreme destruction of the cerebral cortex and subcortical white matter and the calcification, gliosis, and granulomas.



6A 6B

6C 6D

FIG. 6.—Photomicrographs of sections from Cases 1 and 2 showing fungi.

A. Case 1. The refractile, septate, branching hyphae of aspergillus from the granulomatous mass.

B., C., and D, Case 2. Note the fungi of various shapes and sizes. The black masses represent the Hülle cells of aspergillus.

leucocytes, and small blood vessels (Fig. 4c). An increased cellularity and vascularity of the tectum, and an ependymitis of the aqueduct of the Sylvius which contained cellular detritus and an enormous number of fungi, were other striking findings at this level.

Sections of the cerebellum revealed only a mild leptomeningitis with lymphocytes, mononuclears, and a few microglial phagocytes. Loss of Purkinje cells and proliferation of the Bergmann glial cells were noted in a few folia and in one place there was an abscess with centrally placed fungi extending from the meninges into the molecular layer. Similarly, sections through the cerebral hemispheres revealed only a slight thickening of the leptomeninges with moderate infiltration by

mononuclear cells. In the sub-ependymal zone of the lateral ventricle there were small dilated and "cuffed" vessels.

An abundant growth of *Aspergillus fumigatus* was obtained from cultures of the subarachnoid exudate.

Before operation the clinical symptoms were thought to indicate a space-occupying extramedullary lesion of the posterior fossa and upper cervical canal on the left side. Tumour and chronic adhesive arachnoiditis were considered likely aetiological possibilities.

Isolation of the aspergillus was not accomplished while the patient was living, although repeated cultures for fungus were performed on cerebrospinal fluid from the lumbar sac, ventricle, and cisterna magna. Recovery of *Aspergillus fumigatus* at necropsy, however, did not prove that it was the causative agent, for, in view of the known ubiquity of the fungus, the possibility of a post-mortem contaminant or a secondary invader could not be dismissed. We believe the presence of fungi with typical morphology in the centre of abscesses and granulomas, found in both the biopsy specimen and the necropsy material, left little doubt that we were dealing with an example of aspergillus infection of the central nervous system.

In correlating the clinical with the pathological findings it is probable that the burning pain in the right occipital area reflected early involvement of the upper cervical nerve roots. As the disease progressed more roots were implicated, accounting for the pain in the neck and left shoulder, muscular weakness, atrophy, and diminished left biceps reflex. At what stage in the disease the obstruction to the flow of cerebrospinal fluid occurred could not be determined. Presumably, it happened some time before the onset of headache, papilloedema, and diplopia. Since the aqueduct of Sylvius was patent it must be assumed that the hydrocephalus resulted from fibrous thickening of the basilar leptomeninges with obstruction of the foramens of Magendie and Luschka. The lesions responsible for the hydrocephalus were not demonstrated microscopically because adequate sections through the proper levels were not available.

Invasion of the brain-stem occurred in at least two places, yet it was so slight that only minimal symptoms and signs of brain-stem involvement were produced. Pressure effects must also have been minimal since the extrinsic mass, even at the time of death, was not large. It is surprising that there was not more clinical evidence of involvement of the cranial nerves that were implicated in the inflammatory mass.

Outside the central nervous system no sign of aspergillus infection was demonstrated. The symptoms of sinusitis at the onset of the illness suggested one possible route of invasion by the fungus. Another, and perhaps more likely pathway by which the central nervous system may have been infected, is by direct extension from the ear to the base of the brain where the pathological process was localized. Aspergillus is stated to be a common cause of external ear infection (Whalen, 1938). However, since neither the sinuses nor the ears were cultured for fungi at necropsy, the route of entry remains unproved.

Case 2.—A coloured boy, aged 10 months, was brought to the Boston Floating Hospital because of intermittent spasms of the trunk and limbs, rigidity of the hands and arms, and inability to support the head.

The symptoms had begun at the age of 4 months when the patient became unusually irritable. He cried frequently and seemed generally dissatisfied. At about the same time there was the onset of peculiar spells consisting of a sudden shriek with upward turning of the eyes and stiffening and jerking of all four extremities. These occurred as often as six to seven times a day and each attack lasted two to three minutes. The parents were not sure whether or not consciousness was lost during these spells. Thereafter a noticeable change in the patient's behaviour was noted. Whereas he had been lively, had manifested pleasure by cooing and squealing, had held up his head fairly well, had attempted to pull himself to a sitting position, and had been able to manipulate toys, he was now content to lie passively in his crib taking less and less notice of what went on around him. He continued to eat well and cut two teeth. The lower extremities were noted to have become quite stiff; the upper ones less so. In the weeks preceding admission the patient had become quite apathetic.

Birth had been normal at full term and the weight at birth was 5½ lb. His body was well proportioned. He breathed without any delay and responded well during the first days of life. During the first four months the patient's appetite was good; he gained weight and developed as rapidly as two older siblings aged 4½ and 2 years who were regarded as normal. The diet was probably adequate. The family history contributed nothing. No jaundice or haemorrhagic tendency had been observed. In addition to two older siblings there was a third, 2 weeks old, who was also normal.

When first examined after admission to the hospital the patient was noted to be well nourished and about average size for this age. He lay continuously on the side with the neck slightly extended, the arms flexed, and the legs extended. The temperature was 98–99° F., the pulse ranged between 100 to 120, and respiration was 30 per minute. When left alone he lay dormant; if molested in any way he whimpered. The head was of normal size and shape. The anterior fontanelle was flat and measured 2·5 cm. in width. Auditory and visual stimuli seldom evoked any response but touching

or pinching the skin of the face and neck brought about poorly directed squirming movements of all parts of the body. A dangling toy failed to attract his attention but on one occasion his eyes were observed to follow a flashlight and moved conjugately from side to side. The pupils were round and equal and reacted to light promptly. The optic fundi and external ears were normal. One examiner noted that he seemed to hearken when his name was called. He sucked vigorously and retained his food. When pulled to a sitting position his head lolled helplessly indicating, amongst other things, that there was no stiffness of the neck. The skeletal muscles were firm and strong. The arms and legs were spastic, with hyperactive deep tendon reflexes and bilateral extensor plantar responses. Startle caused movements of all four extremities. The limbs were withdrawn from painful stimuli. Tonic neck reflexes were not elicited. There was no abnormality of the spine. The general physical examination was within normal limits except for enlarged tonsils and a grade I systolic cardiac murmur at the third left interspace.

Laboratory Data.—The leucocytic count was 8,900 per c. mm. (34% neutrophils, 48% lymphocytes, 7% eosinophils, 9% monocytes, and 1% blast forms). The red cell count was 5·5 million per c. mm. and the haemoglobin 14 mg.%. Urine analysis disclosed no abnormal findings. The cerebrospinal fluid contained 60 mg. of protein and 69 mg. of sugar per 100 ml. No cells were seen and the Hinton test was negative on the blood and cerebrospinal fluid. On culture of the cerebrospinal fluid there was no growth of bacteria or fungi after four days. Fluid from the subdural space contained 38 mg. of protein per 100 ml. and there were no cells. Radiographs of the chest and hips were not remarkable, but those of the head revealed several radio-opaque densities within the substance of both cerebral hemispheres (Fig. 1A). A toxoplasmin skin test was performed on the infant and his mother. The infant did not show any reaction, but the mother had a questionably positive one.

Course—The patient was placed under observation for 22 days during most of which time he remained in the same stuporous, fretful state. A survey by a psychometrist revealed that only 4 and 6 weeks' tests could be accomplished but testing was so difficult that the results were not thought to be reliable. A pneumoencephalogram was done but had to be discontinued because of a generalized convulsion. The lateral ventricles were dilated and air had accumulated in the subdural and subarachnoid space in amounts suggestive of atrophy of the brain (Fig. 1A). An electroencephalogram showed slow asynchronous waves of high voltage in all leads without a trace of alpha rhythm and was interpreted as abnormal.

The patient's condition changed relatively little during the hospital stay and he was discharged unimproved. In the following two weeks he failed rapidly, became pale, stuporous to semicomatose, and unable to take nourishment. On the morning of December 8, 1948, he was admitted to the Boston City Hospital but died 15 minutes after admission, before any further examination could be carried out. He was 11 months of age at death.

Post-mortem Examination.—A necropsy was performed approximately 26 hours after death. At this time general nutrition and development of the body were judged to be within normal limits. There were no abnormal findings outside the central nervous system. Microscopic examination of the lungs, liver, spleen, heart, kidneys, gastro-intestinal tract, and bone marrow revealed normal findings.

The brain was of average size but grossly abnormal. There were numerous fibrinous adhesions between the cranial dura and the arachnoid membrane. In many places, particularly the central portions of the right cerebral hemisphere, the right temporal lobe, and the left frontal and occipital lobes, the brain tissue was destroyed and replaced by numerous cavities. These cavities ranged from a few millimetres to 2·5 cm. in size, were separated by strands of connective tissue, and contained a grey, gelatinous fluid that clotted on formalin fixation (Figs. 2A and 2B). The cerebral cortex in many of the affected areas was reduced to a thin, grey membrane, and the adjacent arachnoid was thickened and slightly opaque. The tissue between the cavities was grey-brown.

On frontal section the lesions were observed in both grey and white matter. The claustrum and putamen were involved in at least one place. The lateral ventricles were dilated but their walls appeared to be intact. Sections of the brain-stem and cerebellum revealed that the pyramids were smaller than normal and greyish. No lesions were seen in this part of the brain.

Upon microscopic examination it was found that in several sections of the cerebral cortex there was a thickening of the leptomeninges and a moderate amount of cellular exudate in the subarachnoid space. Most of the cells were either lymphocytes or large monocytes, but occasional plasma cells and multinucleated macrophages were seen. The exudate was denser in the depths of the sulci than over the surface of the cortex. There was a thick layer of glial cells in the cerebral cortex just beneath the pia. In the depths of the cortex numerous granulomatous foci, either single or conglomerated into large granulomatous zones (Figs. 5B and 5C), were seen. The centre of the small granulomas was formed of a single or rarely more than one foreign-body giant cell, containing as many as 20 to 30 nuclei, and epithelioid cells. Fibroblasts surrounded them and in the periphery there were numerous lymphocytes, a few plasma cells, microglial histiocytes, and monocytes. The larger granulomas contained a mixture of fibroblasts and numerous giant cells and inflammatory cells. An interesting finding was the presence of a large number of blue-staining rods which under high magnification appeared tubular. They were indistinctly septate and in places were branched; many of them had bulbous ends. They were gathered in tangled masses or were present singly, and in certain sections a collection of rounded blue bodies, resembling the bulbous terminations of these rods, was seen. These structures were present in the centres of the

granulomas and were free in the adjacent cortex (Figs. 6B, 6C, and 6D). Also, large hyaline oval or round bodies with translucent borders were encountered. These bodies (Hülle cells) were seen both within and adjacent to the granulomas (Fig. 6C). The blood vessels around the lesions did not appear to be affected, but calcification of the media and subintimal layer was seen in some and easily confused with the aforementioned rods. Calcified particles (Fig. 5A) were found near many of the granulomatous masses. This calcification was most dense in areas where the lesions were fibrotic. The numerous cavities contained an amorphous pink-staining material. In regions where the lesions were present all of the neurons had disappeared, leaving behind only a framework of proliferated astrocytes. The underlying white matter showed cavitation, loss of myelin, and a fibrous gliosis.

Frontal sections through the basal ganglia disclosed similar lesions in the claustrum, the external capsule, putamen, internal capsule, and, to a slight extent, in the thalamus, subthalamus, and midbrain. The ventricles were not involved, and the ventricular ependyma and choroid plexuses were normal. There were no lesions in the lower part of the brain-stem, cerebellum, or spinal cord.

Sections through the dura mater revealed a partially organized haemorrhage on its inner surface.

The fresh brain material was inoculated in several laboratory animals none of which ever developed lesions of toxoplasmosis. Routine cultures for bacteria were also negative. No attempt was made to culture a fungus because this possibility was not considered at the time of necropsy.

Clinically this patient was apparently normal till about the age of 4 months when the behavioural regression and epilepsy began. Throughout the entire course of the illness there were signs of pyramidal tract disease bilaterally, in the form of weakness and spasticity of the legs and to a lesser extent of the arms. These facts when considered with the cerebral calcifications, abnormal electro-encephalogram, and elevated cerebrospinal fluid proteins suggested clinically that the disease process involved both cerebral hemispheres, and was probably in the nature of a meningo-encephalitis. Toxoplasmosis was considered the most satisfactory aetiological explanation, despite the lack of family history and negative skin tests.

At necropsy the findings were those of a chronic granulomatous meningo-encephalitis. Microscopically the lesions differed from those of toxoplasmosis described by several authors (Wolf and Cowen, 1937; Wolf, Cowen, and Paige, 1939). The presence of well-formed granulomatous giant cells and the absence of any changes in the ependyma and choroid plexuses were clearly inconsistent with a toxoplasmic encephalitis. The examination of numerous sections of the brain and other organs failed to reveal toxoplasma. The retinae were not available for microscopic study but had been normal upon opthalmoscopic examination. Furthermore, inoculation of the brain tissue of the patient into laboratory animals failed to produce toxoplasmosis.

Tuberculosis and syphilis were excluded as possible causes of the pathological lesions, because caseation necrosis did not occur in any of the lesions, particularly the large ones, and there was no arteritis in the vessels about the lesions. Also against syphilis was the absence of involvement of extraneural tissues and the negative Hinton and Wassermann tests.

The tangles of blue-staining rods in and around the lesions were identified as fungi belonging to the group of *Hyphomycetes*, and the presence of the hyaline cells, which were later identified as Hülle cells (Thom and Raper, 1945), strongly suggested their being aspergilli. A mycologist, Dr. George Foley, kindly examined the sections and reported to us that the morphology of the septate hyphae with conidiophore structures and mycelia is characteristic af aspergillus. He stated that the large densely stained rounded bodies surrounded by a capsule-like halo were probably Hülle cells of aspergillus. The exact origin and function of these cells is unknown.

The chronicity of the lesions in this case indicated that they may have been present before the onset of symptoms. It is interesting to speculate whether this could be an instance of intra-uterine infection. Cases of aspergillus infection of the genital tract have been recorded (Goldstine, 1933; Weinstein and Lewis, 1938). However, the mother exhibited no signs of this disease and birth was normal.

Very little can be said about the route of entry of the fungus into the brain. In view of the negative findings in the rest of the body there was no evidence of the infection being metastatic from some other organ. The sinuses and ears were not cultured for fungi at necropsy though they were grossly normal. It is possible that the ear or nasal sinuses were the portal of entry.

Discussion

Recorded examples of cerebral aspergillosis are few. Moniz and Loff (1931) reported the case of a 44-year-old woman in whom a complete right hemiplegia developed in 17 days. The cerebrospinal fluid was under normal pressure; there were 60 cells per c. mm., and the total protein was increased. At necropsy a large abscess was found in the left frontal lobe. Fungi, morphologically resembling aspergilli, were found in this abscess, but they were not cultured. The remainder of the

post-mortem examination was negative. In view of the past history of corneal ulcer, the authors assumed that the fungus had entered the brain through the eye.

An aspergillus abscess and granuloma of the right frontal lobe was the subject of a report by Just (1931). The patient, a 52-year-old man, had had the clinical symptoms of a space-occupying lesion. Two operations were performed and at the second a culture of aspirated fluid revealed a pure growth of *Aspergillus fumigatus*. At necropsy the only significant finding was a lesion in the right frontal lobe. The orbital plate of the frontal bone on the right side was eroded in several places. Just considered that the infection had extended directly from the nose and frontal sinus through the frontal bone to the brain.

In 1935 Guillain, Bertrand, and Lereboullet described a case in which an abscess of the brain was presumably caused by aspergillus. The patient, a 33-year-old woman, presented the symptoms of a sphenoidal fissure syndrome on the right with pyramidal tract signs on the left. The disease had evolved over a period of one year. After various unsuccessful therapeutic measures she died, and at necropsy an abscess of the right frontal lobe was found. This abscess was surrounded by a dense, collagenous connective-tissue zone, and filamentous hyphae resembling aspergilli were found in the centre of the abscess. No culture was performed. There was localized chronic meningitis at the base of the skull, and the nerves in the right sphenoid fissure and the contents of the right orbit were involved in the pathological process. The authors stated that the fungus entered the cranial cavity by direct extension from the orbit.

Acute aspergillus meningitis in a 19-year-old man was reported by Linck (1939). His patient died five days after the onset of symptoms and at necropsy there was an acute exudative meningitis with several small granulomatous lesions along the Sylvian fissures. Mycelial threads which were identified as aspergillus were found in the centre of these granulomas. Cultures of the cerebrospinal fluid and meningeal exudate were not obtained.

The first case of generalized aspergillosis with involvement of the central nervous system was published by Cawley (1947). The patient, an 8-year-old child, had been ill since the age of 6 weeks with a chronic intermittent respiratory disease. He developed a multiloculated abscess of the right chest wall from which *Aspergillus fumigatus* was cultured. At the age of 7½ years signs of involvement of the cerebellum appeared, and a right cerebellar abscess was evacuated by operation. Following this, numerous abscesses formed all over the body and the patient finally succumbed. The necropsy revealed abscesses of varying size in the dura, brain, heart, lungs, mediastinum, lymph nodes, spleen, liver, right kidney, and right ankle. *Aspergillus fumigatus* was cultured from all the lesions at necropsy. It was concluded that the infection began in the lungs early in life and that the later clinical manifestations were the result of metastases.

A second instance of probable generalized aspergillosis, in a 22-year-old man, was recently reported by Grekin, Cawley, and Zheutlin (1950). The anatomical evidence of cerebral involvement is not convincing but a full pathological description of the case was not recorded.

McKee (1950) recorded the case of a basal meningitis in a 69-year-old man who had had symptoms of meningeal involvement for about two months. Several examinations of the cerebrospinal fluid revealed pleocytosis and an increase in the total protein content but cultures of the fluid were repeatedly negative. At necropsy a yellowish exudate was found at the base of the brain, and also in the sphenoid sinus. Upon microscopic examination there was chronic inflammation with large numbers of branching hyphae in both the brain and the wall of the sphenoid sinus. Cultures obtained after death, however, yielded only haemolytic *Staphylococcus albus*. McKee believed that the infection had spread directly from the sphenoid sinus to the base of the brain.

Cases of osteomyelitis of the base of the skull with a secondary localized granulomatous infection in the adjacent meninges have been reported by Nicod (1946) and Schnyder (1948). The last author quotes similar cases recorded by Oppe, and Wätjen. Fungi in the lesions of all these cases were identified morphologically as aspergilli, but they were not confirmed by culture.

Recently Wybel (1952) reported a pathologically verified case of aspergillus infection involving the meninges of the cervical spinal cord. His case is of particular interest in that the affection followed pneumococcal meningitis treated with intrathecal penicillin three years before.

Pathological Features.—In reviewing the cases that have been recorded in the literature, as well as the two cases of aspergillosis mentioned here, it becomes obvious that the pathological reaction in the nervous system takes the form of a chronic suppurative or granulomatous inflammation. The case reported by Linck (1939) is an exception, for in his case the organisms produced acute exudative meningitis with a predominantly polymorphonuclear reaction in the

cerebrospinal fluid. It is also evident that the lesions may be localized either in the meninges or in the brain, the site depending upon the route of entry of the fungus. Even in the case where haematogenous dispersal of the fungi was proved (Cawley, 1947) the lesion took the form of localized abscesses in the cerebellum and in the meninges.

The cases quoted by Moniz and Loff (1931), Just (1931), Guillain and others (1935), Schnyder (1948), Nicod (1946), Wybel (1952), and our first case are examples of a localized productive inflammatory lesion. Our case is interesting in that the granulomatous meningeal mass was strictly localized to the posterior fossa and upper cervical spinal canal and produced the clinical picture of a slowly growing mass or an arachnoiditis involving the meninges and cervical roots. Similar clinical and pathological examples have been mentioned by Schnyder who cites cases of Wätjen and of Oppe. In their cases the primary lesion was a mycotic osteomyelitis of the base of the skull, with extension to the adjacent meninges and the formation of a localized meningeal granulomata; Schnyder's case was mistaken clinically for tic douloreux because involvement of the Gasserian ganglion by the inflammatory mass had led to severe pain in the trigeminal distribution.

Our second case differs from others in that the brain was diffusely involved and pathologically the disease took the form of a granulomatous encephalitis with only a moderate reactive meningitis. The fungi had produced lesions over wide areas of the cerebral cortex and basal ganglia. These lesions had evolved slowly and permitted a dense fibrous gliosis with calcification to occur. Despite extensive involvement of the cerebral hemispheres there were no granulomatous lesions in the brain-stem and cerebellum. In a sense, therefore, the lesions, though diffuse, were localized in the cerebral hemispheres.

Mention should be made of the extensive calcification in the brain of the infant reported here. This led to the erroneous clinical diagnosis of toxoplasmosis, a condition in which cerebral calcification is quite common (Dyke, Wolf, Cowen, Paige, and Caffey, 1942). Calcifications of the brain may be encountered in a variety of other conditions (Courville and Adelstein, 1930). Calcifications in tuberculomata have been reported (Evans and Courville, 1938), and calcification in torulosis of the newborn has been reported by Neuhauser and Tucker (1948). Intracranial calcification following coccidioidal meningitis (Reeves and Baisinger, 1945) has also been reported. So far as we can determine calcification in aspergillus meningitis or encephalitis has not been described previously.

The possibility of this case being one of toxoplasmosis with secondary aspergillus infection was given serious consideration, but thought to be unlikely. A careful search of the lesions failed to demonstrate toxoplasma, but, more important, the character of the calcified and granulomatous lesions did not resemble those of toxoplasmosis.

Pathogenesis.—Deep fungus infections in general are known to produce either a chronic suppurative or granulomatous inflammatory response in tissue (Baker, 1947). The mechanism whereby fungi evoke this reaction is not fully understood, but it has been postulated that they act either as large foreign bodies or produce lesions by liberating toxic products. Henrici (1939) has demonstrated an endotoxin in *Aspergillus fumigatus*. Subcutaneous injection of this toxin into laboratory animals results in a severe local tissue necrosis and oedema. On intravenous administration degenerative and necrotic changes are seen in the liver and kidneys. The pathological changes in human aspergillosis, however, do not resemble those produced by the endotoxin in animals, but present, instead, the appearance of a foreign body reaction. Nevertheless, the variable reactions in individual cases raises the possibility of other mechanisms, as yet unknown, by which the observed tissue response is produced. The variability of pathological changes is illustrated in such different reactions as the acute exudative meningitis reported by Linck (1939) and the chronic fibrotic or calcific granulomatous lesions seen in the two cases reported here.

An interesting feature observed by Nicod (1946), Schnyder (1948), and McKee (1950) was the implication of the carotid artery by a granulomatous lesion. A similar type of involvement by *Mucormyces* was observed in the cases reported by Gregory, Golden, and Haymaker (1943) and LeCompte and Meissner (1947).

There has been much speculation and little actual data as to the route of entry of the fungi into the brain. Of the cases that have been reported in the literature only the one described by Cawley (1947) convincingly demonstrates a metastatic spread of the fungus to the brain. In his case fungi were demonstrated after death in the heart and lungs. Extension from the eye (Moniz and Loff, 1931), the orbit (Guillain and others, 1935), paranasal sinuses (Just, 1931; McKee, 1950; Nicod, 1946), lungs (Linck, 1939) have all been postulated but the pathological data often fail to establish the pathway. The route of entry of the fungus in the two cases reported here could not be definitely specified.

Wybel (1952) discusses the possible relationship, in

his case, between intrathecal penicillin therapy and the development of cervical meningeal aspergillosis. He concludes that the growth of the fungus was enhanced by penicillin, and cites some evidence from the literature to support this view. In any event, lumbar puncture provided a probable route of entry for the fungus.

Clinical Features.—From the available clinical data it may be stated that aspergillosis of the central nervous system may result in several different syndromes. In seven of the 12 recorded cases there have been symptoms and signs of a solitary, localized, space-occupying intracranial lesion. In five of these the signs pointed to a disorder of the frontal pole of the cerebrum and in two to a posterior fossa lesion. Evidence of disease of retro-orbital structures, i.e. exophthalmos, ocular muscle palsies, amblyopia, and trigeminal nerve dysfunction, were observed in three of the five cases with involvement of the frontal lobes. In one case (Moniz and Loff, 1931) symptoms evolved over 17 days, but the others were chronic. Culture of the spinal fluid was attempted in only one of these cases and no growth was obtained. Lumbar punctures were performed on only three of the above cases and in each of them there were pleocytosis and elevated protein content.

Of the other five cases, one had clinical signs of acute leptomeningitis which led to death in five days, and another of a more chronic meningitis of several months' duration. In the case of Grekin, Cawley, and Zheutlin (1950) there was generalized aspergillosis and the symptoms of meningitis developed terminally. In one instance the disorder presented as a spinal cord tumour. Our second case is unique in that the principal clinical symptoms indicated cerebral disorder with dementia, seizures, and spastic paralysis of the arms and legs, and the onset of the disease was either prenatal or during the first few months after birth. The cerebrospinal fluid was not cultured in most of the cases of meningitis. It is probable that the organisms could have been recovered if this had been done.

Summary

Two new cases of aspergillus infection of the central nervous system are reported. In the first of these the symptoms, like those of several other previously published cases, were consistent with a chronic, localized granuloma of the meninges of the cervical cord and brain-stem. The second presented as chronic encephalitis with progressive dementia, convulsions, spastic paralysis, and cerebral calcification. The clinical manifestations, mycology, pathogenesis, and pathology of these and the other reported cases are discussed.

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THE LOCALIZATION OF ANEURIN PYROPHOSPHATASE IN THE BRAIN

BY

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Vitamin B_1 is nearly exclusively present in animal tissues as aneurin pyrophosphate (Ochoa and Peters, 1938). The vitamin is first converted to aneurin pyrophosphate by the tissues and in this form it enables the oxidative decarboxylation of pyruvic acid to take place allowing glucose metabolism to go beyond the pyruvate stage (Banga, Ochoa, and Peters, 1939). It has been shown more recently that aneurin pyrophosphate participates in other metabolic processes in nervous tissue (Green, Stumpf, and Zarudnaya, 1947). With regard to pyruvate oxidation, Banga and his colleagues (1939) found that free aneurin is more effective than aneurin pyrophosphate in stimulating the respiration of brain preparations from vitamin B_1-deficient animals. A possible explanation of this finding is that the tissue is poorly permeable to aneurin pyrophosphate but more permeable to aneurin. Aneurin consequently is able to pass the permeability barriers, become phosphorylated and be available to act as the co-enzyme. This view presupposes some dephosphorylating mechanism in the living animal whereby aneurin pyrophosphate is degraded to free aneurin.

The dephosphorylation of aneurin pyrophosphate by brain tissue was observed by Ochoa (1939). Westenbrink, Parvé, and Goudsmit (1943) described an active phosphatase hydrolysing the phosphoric esters of aneurin. It was found that this enzyme successively removes the two phosphate groups from aneurin pyrophosphate, so that when the terminal phosphate is removed, aneurin orthophosphate appears as the intermediary which is further broken down, releasing aneurin.

The histological demonstration in brain tissue of the sites of this hydrolytic process is of interest in relation to the pathology of those nervous diseases associated with aneurin deficiency.

This paper describes and illustrates the results obtained from localizing in brain tissue the sites of enzymatic cleavage of phosphate from aneurin pyrophosphate at *p*H 6·9.

Method

Normal, young, adult male and virgin female white rats were used. The brains were removed rapidly under ether anaesthesia, sliced into 2 mm. coronal sections, frozen at −65°C in isopentane, and dried under vacuum. The procedure employed for the preparation of sections was in no way different from that previously described for the localization of the sites of activity of phosphatases (Naidoo and Pratt, 1951). The site of enzymatic cleavage of the phosphoric acid ester used as the substrate was demonstrated by the precipitation of the liberated phosphate as an insoluble lead salt at the site of action. The lead phosphate was converted to dark brown lead sulphide, the distribution of which was studied under the microscope.

The most suitable substrate medium for the incubation of sections was constituted thus :

0·1 M sodium maleate buffer (*p*H 7·1)	15 ml.
0·005 M stock solution aneurin pyrophosphate ..	3 ml.
0·1 M magnesium chloride	6 ml.
0·04 M lead acetate	0·75 ml.
Water to	30 ml.

The final *p*H was between 6·8 and 7·0.

Media were prepared freshly before use. Stock solutions of substrates were neutralized with NaOH and stored at −78°C. The other constituents were either of analytical grade or were recrystallized. Glass-distilled water was used throughout. The aneurin pyrophosphate used was obtained from Roche Products (cocarboxylase), and was specified as being virtually free from other phosphorylated derivatives of aneurin. Samples used in this work were re-precipitated twice by solution in a little N–HCl and the addition of 5 volumes of acetone. Re-precipitation did not lead to any discernible change in the histological results, nor did an independently prepared specimen for which we are indebted to Dr. A. L. Morrison of Roche Products Ltd.

The aneurin orthophosphate solution was prepared from aneurin pyrophosphate. Aneurin pyrophosphate (100 mg.) was hydrolysed by heating in a sealed tube with N–HCl (3 ml.) for 30 minutes at 100°C., brought to *p*H 6·8 with N–NaOH, and M–$BaCl_2$ solution (1 ml.) added. The barium phosphate precipitate was discarded and excess barium ions removed by the addition of a slight excess of 1% Na_2SO_4 solution. The precipitate was discarded and after phosphate analysis the solution was diluted to contain 155 μg. of organic phosphate per ml.

Control of the tissue activity could be obtained by omission of the phosphoric acid ester from the medium and by heating the sections in steam before incubation or by treating them with trichloracetic acid. In all these cases, and also when the magnesium salt was omitted from the medium, the staining was negligible. The intensity of staining was greatly reduced if uranyl acetate (10^{-4}M) was added to the medium, but sodium fluoride (10^{-3}M) produced no effect.

When the medium described above was used, characteristic staining was recognizable after 10 minutes' incubation, and slides were removed at intervals up to 80 minutes. If the aneurin pyrophosphate in the medium was replaced by a similar concentration of either aneurin orthophosphate or of inorganic pyrophosphate, the results were negative in each case for a comparable range of incubation times. Positive results were obtained only after incubation periods of five hours or longer. If the *p*H of the aneurin pyrophosphate medium was varied over a range from 5·0 to 8·0, a similar type of staining to that usually seen was observed, but the intensity reached in a given time was reduced, especially at the more acid *p*H values.

Results

The findings described represent the sites of lead sulphide deposition at the points of phosphate liberation from aneurin pyrophosphate in 10 consecutive animals.

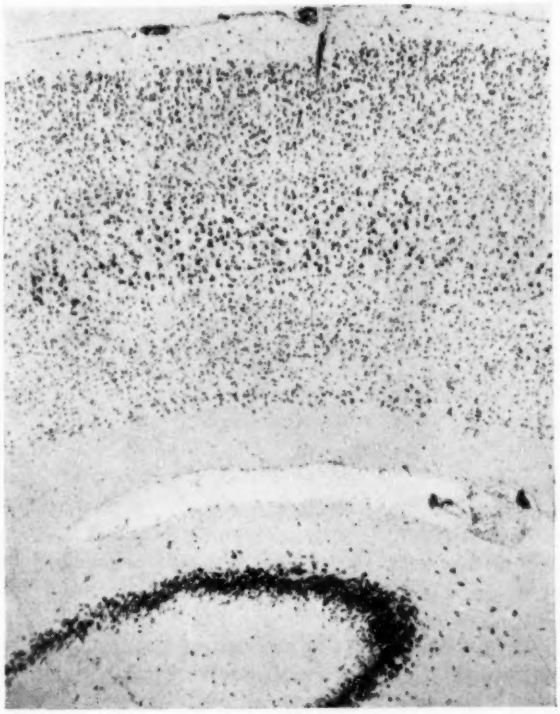

FIG. 1.—Cerebral cortex showing deep staining of the nerve cell bodies and glia. × 30.

The cerebral cortex showed the characteristic cytoarchitecture. The cell bodies were clearly demarcated throughout the whole brain and frequently layers III and V of the cerebral cortex were prominent, appearing more deeply stained than the other layers. The cortex in a coronal section through the optic chiasma showed layers II and V as the most deeply stained (Fig. 1). The degree of staining of the cortical layers, however, appeared to vary from region to region. The whole cortex gave the impression of a good Nissl cresyl violet preparation with the differences in the depth of staining more than usually marked. The cell cytoplasm, nucleus, and nucleolus were stained but in uneven degree, the cytoplasm and nucleolus being more deeply stained than the nucleus. The cytoplasm did not stain evenly throughout but amorphous aggregates of deeply staining material were evident in some cells at the periphery and in others around the nucleus. It was not clear from an examination of the frozen dried material whether or not these aggregates represented Nissl bodies. The nucleus itself showed a light, more even deposit of lead sulphide but scattered throughout the nucleoplasm were small discrete granules of highly stained material. The nucleolus was consistently the darkest structure in the cortical cell body. Cells of layer V frequently showed deep staining for a short distance along their dendrites.

The nerve cell bodies in the hippocampal formation (Fig. 2), the habenula, the striatum, thalamus and hypothalamus (Fig. 3) stained deeply. The most deeply staining nerve cells in these regions were those of the hippocampus, the large cells of the globus pallidus and of the putamen (Fig. 4), and the paraventricular nucleus of the hypothalamus. The nucleus supraopticus and the mammillary nuclei stained deeply and were demonstrable after the shorter incubation periods, but their depth of staining was not as great as that of the fascia dentata of the hippocampus. The cells of the amygdaloid nuclei were consistently deeply stained.

In the midbrain, pons, and medulla nerve cells stained more lightly than the cells of the cerebral cortex, except for the nerve cells of the periaqueductal grey matter which stained deeply. Nerve cell bodies of the cranial nerve nuclei were lightly stained and were recognizable as pale brown cell bodies at an incubation time of 40 minutes.

In the cerebellar cortex the Purkinje cells and the Bergmann glia stained selectively (Fig. 5). The earliest cerebellar cells to show staining were the Bergmann glia, but after the usual incubation period of 40 minutes the Purkinje cells reached an equal depth of staining.

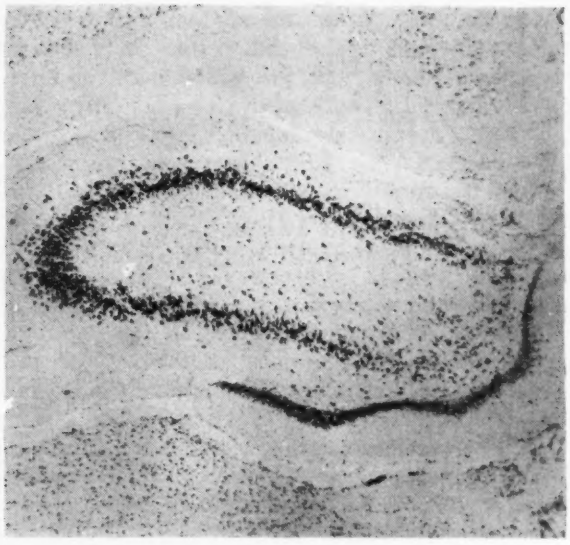

FIG. 2.—Hippocampus : cell bodies of the hippocampus (pyramidal layer and dentate gyrus) stain deeply. × 30.

FIG. 4.—Lentiform nucleus : the large cells of the globus pallidus and putamen are prominent. × 30.

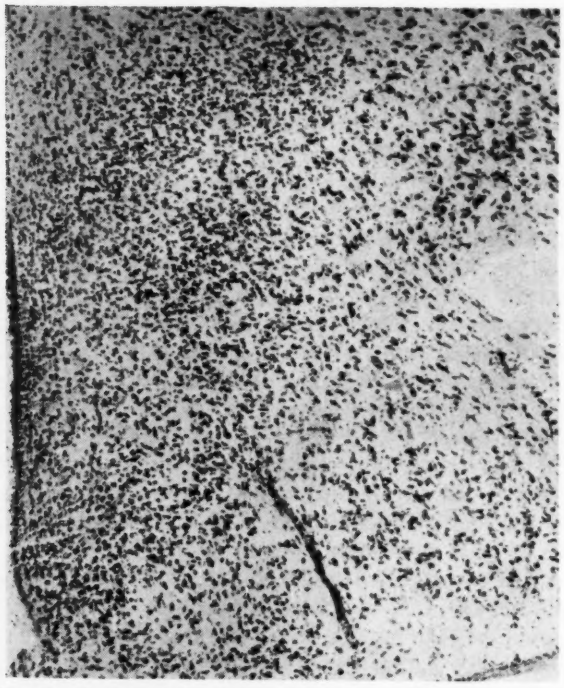

FIG. 3.—The hypothalamic nerve cells stain more deeply than those from other regions of the brain except the hippocampus. The larger intracerebral vessels show deep intimal staining. × 35.

FIG. 5.—Large artery at the base of the brain showing staining of the intima and lamina elastica. × 100.

Glial cells were stained deeply throughout the whole brain. Microglia and oligodendroglia wherever seen were intensely stained, but astrocytes varied in their degree of staining even after prolonged incubation times. The endothelial nuclei of the choroidal capillaries stained moderately but the choroidal cells did not stain. Ependymal cells lining the ventricles were lightly stained. The parenchymal capillaries did not show staining but the larger intracerebral and extracerebral vessels

FIG. 6.—Cerebellar cortex : the Purkinje cells and Bergmann glia are the only structures which stain deeply. × 50.

showed deep staining of the intima and the lamina elastica (Fig. 6). Throughout the intima of these vessels were deeply stained, small, discrete granules.

Discussion

That the localizations described represent the sites of enzyme action has been established with a fair degree of certainty by the absence of staining when aneurin pyrophosphate is omitted from the incubation medium ; by the suppression of staining when the magnesium ions are omitted, or when a low concentration of the inhibitor uranyl acetate is added ; and by heating or chemical treatment of the sections before incubation. The change seen in the localization of staining due to the replacement of the aneurin pyrophosphate by another phosphoric acid ester, such as 5-adenylic acid, provides further confirmatory evidence that enzymatic dephosphorylation of aneurin pyrophosphate has been demonstrated. It precludes the possibility of the pictures being produced to any appreciable extent by the deposition of the precipitate on foci of crystallization within the tissue (Naidoo and Pratt, 1951).

The activity detected in the present investigation appears to be distinct from that of non-specific phosphatases demonstrated by glycerophosphate. This activity has not been found in nervous tissue by previous workers who have used aneurin pyrophosphate as a substrate, presumably on account of their less favourable fixation methods.

The localizations obtained by the incubation of frozen dried brain tissue with aneurin pyrophosphate at *p*H 6·9 show certain similarities to those obtained with glycerophosphate at *p*H 5·3. But there are chemical and histological differences.

Tissue incubated with aneurin pyrophosphate at *p*H 5·3 or with glycerophosphate at *p*H 6·9 stains in each case at a greatly reduced rate. This difference in the *p*H optima, possibly explicable by differences in the physico-chemical properties of the two substrates, is large enough to suggest that it is an integral part of the conditions necessary for the demonstration of separate enzyme activities. Fluoride suppresses staining in the glycerophosphate medium but has no effect on the rate of staining when aneurin pyrophosphate is used. When magnesium ions are omitted from the medium, staining is completely absent in the aneurin pyrophosphate medium but only reduced in rate when glycerophosphate is employed. It appears likely that the reaction demonstrated is the splitting of aneurin pyrophosphate to aneurin orthophosphate since replacement of the aneurin pyrophosphate in the medium by aneurin orthophosphate or by inorganic pyrophosphate fails to produce positive results within the normal incubation period.

Although there is a similarity between the picture obtained with aneurin pyrophosphate and that with glycerophosphate, some histological differences are present. In the cerebral cortex layer VI is much less prominent than in glycerophosphate material and the nuclei of neurons do stain. The cells of the cranial nerve nuclei are more lightly stained than corresponding cells in glycerophosphate sections. In the cerebellum basket fibres, which stain with material incubated with glycerophosphate, do not appear. Bergmann glia, which do not stain in sections incubated with glycerophosphate, appear first and stain most deeply of all cerebellar structures. Similar intense staining of the Bergmann glia is found when adenosine triphosphate is used as the substrate. The choroid plexus stains moderately in contrast to the deeper staining found when glycerophosphate is used. A feature which appears in the aneurin pyrophosphate material but not in glycerophosphate incubated sections is the intimal staining of the larger vessels and arterioles. The discrete and granular appearances in the intima, however, do not necessarily indicate a particulate distribution of the enzyme.

The significance of these histological and biochemical differences is not immediately apparent.

Although it is well established that aneurin pyrophosphate functions as a co-enzyme, the mechanism of its action is not clear. The biochemical study by Westenbrink and his colleagues of the breakdown by an alkaline phosphatase of aneurin pyrophosphate in a wide range of animal tissues does not directly assist in the interpretation of the present results. Further, these authors find that aneurin orthophosphate is split readily by this phosphatase, whilst the process now studied histologically in brain appears to be concerned more directly with the hydrolysis of aneurin pyrophosphate to aneurin orthophosphate and to be distinct from the action of non-specific phosphatases. Investigation of the conditions under which aneurin orthophosphate is hydrolysed to aneurin by brain tissue sections and the demonstration of the sites of this hydrolysis would be of value.

Banga, Ochoa, and Peters (1939) find that the greater effectiveness of aneurin compared with that of aneurin pyrophosphate in stimulating the respiration of brain slices from aneurin-deficient animals can be explained by the failure of aneurin pyrophosphate to penetrate into the tissue. As aneurin is the diffusible form, at some stage dephosphorylation may be essential to the assimilation or further utilization of the vitamin. Thus sites of intense aneurin pyrophosphatase activity may indicate loci of high vitamin B_1 requirements. Alternatively, the enzyme localized at these sites may function in some more complex process specific to the vitamin but of a nature not yet understood. Although further anatomical study is necessary to determine in detail the degree of hydrolysis of the co-enzyme taking place in the various structures of the brain, it is of interest at this stage to note that the hypothalamus in general stains very deeply.

Summary

The sites of hydrolysis of aneurin pyrophosphate (cocarboxylase, vitamin B_1 pyrophosphate) have been demonstrated in frozen dried normal rat brain. The histological sites at which this activity is localized and the biochemical conditions in which it can be demonstrated differ from those previously described when other phosphoric acid esters were used as substrates.

We are indebted to the Bethlem Royal Hospital and the Maudsley Hospital, and to the Medical Research Council (Mapother Bequest) for grants made in aid of this research. We wish to thank Professor Alfred Meyer and Dr. H. McIlwain for their interest in the work and Miss Joyce Hinton for her capable technical assistance.

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WOUNDS OF THE VISUAL PATHWAY

PART II: THE STRIATE CORTEX*

BY

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The representation of the visual field in the striate cortex (calcarine cortex, area 17) has received considerable attention. It is agreed that central vision is predominantly represented posteriorly and peripheral vision predominantly anteriorly, but the detailed representation is debated. Holmes (1918) from his study of head injuries in the first world war concluded that concentric zones from the fixation point to the periphery are represented serially in that order from the posterior to the anterior part of the calcarine cortex. Brouwer (1934) took the same view except that he believed that the area devoted to central vision protruded forward a considerable distance as a tongue in the intermediate part of the striate cortex between its upper and lower margins. German and Fox (1934) suggested that the central vision, though predominantly represented posteriorly, is also represented to some extent diffusely throughout the striate cortex.

In cases of complete hemianopia "macular sparing" is often observed, and it is said, though with scanty evidence to support it, that macular sparing occurs in lesions of the occipital lobe but not in lesions of the temporal or parietal lobes. From this comes the chief support for the view that some of the fibres subserving central vision arise in one lateral geniculate body and cross in the corpus callosum to the opposite occipital lobe, so that "the macula" is bilaterally represented.

This paper reports some of the visual field defects which occur in gunshot wounds of the striate cortex, with particular reference to the anatomical deductions which may be made from them. Evidence is presented to indicate in what part of the striate cortex central vision is represented, whether it is represented bilaterally or unilaterally, and how large is the area of cortex devoted to it.

Material

The material is taken from a series of 958 cases of penetrating head injuries, mainly gunshot wounds. One hundred and eighty-eight of these had defects in the visual field attributable to injury of the visual radiation or striate cortex, and this paper is concerned with the 72 cases in which there was a lesion primarily affecting the striate cortex. This material overlaps with that reported by Symonds (1945), whose Case 7 is the same as the present Case 2. The visual fields were plotted with 3/330 and 2/2000 white isopters and also in abnormal areas with 20/2000 white isopter. Except where otherwise stated dense black represents a scotoma to 20/2000, and cross hatching a scotoma to 2/2000. The interval between injury and examination is shown on each chart. In the tracings of radiographs a coarsely hatched area indicates a bony defect in the skull and dense black a radio-opaque foreign body.

Fig. 1 shows the representation of the visual field in the striate cortex seen from the posterior and medial aspects. This map, though similar in many respects to those made by previous observers, has been modified and amplified as the cases described below demand. It is presented at this point rather than after the description of the cases on which it is largely based because interpretation of the cases is very much simplified by reference to it. In the visual field the different parts of the upper quadrant are indicated by numbers, the lower by letters. In both quadrants each series runs from centre to periphery so that any one series (e.g. i, ii, iii, 1, 2, 3, or A, B, C) indicates a sector, whereas corresponding symbols from adjoining series (e.g. ii, II, 2, c, C, γ) indicate an arc of the visual field. The hatched area in the diagram of the striate cortex is that part forming the walls of the calcarine fissure, shown as though the lips of the fissure had been pulled apart. The stippled area represents that part of the striate cortex which is on some aspect of the posterior pole of the occipital lobe and faces either posteriorly or postero-medially, and the area which is neither hatched nor stippled is that part which is in apposition, the falx alone intervening, with the corres-

* The first section on the optic radiation appeared on p. 99 of the previous issue

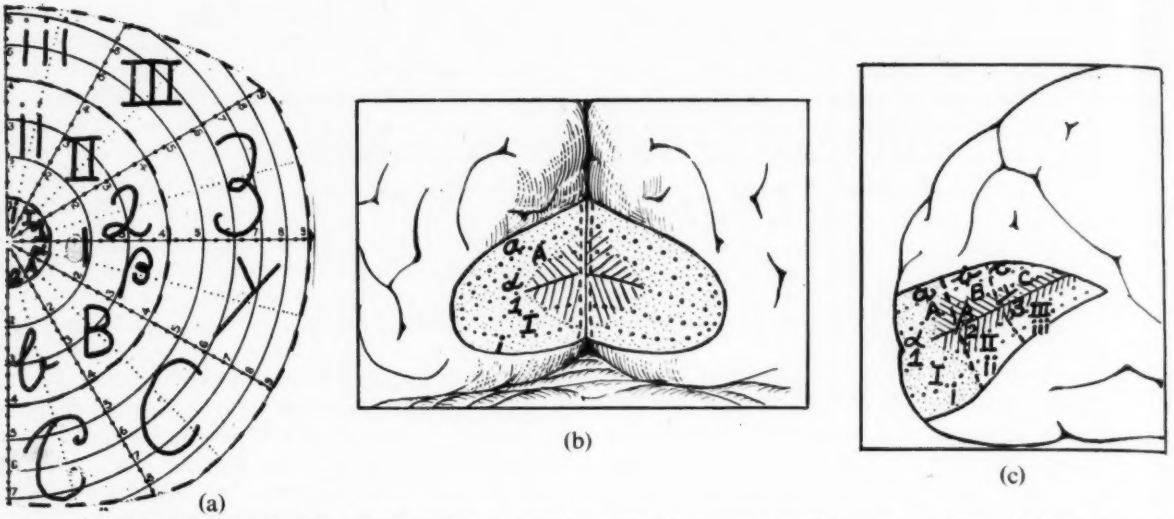


FIG. 1.—Right half visual field (a) and its representation in the striate cortex shown from the posterior (b), and the medial (c) aspects. The hatched area of the striate cortex represents the walls of the calcarine fissure illustrated as though it were pulled open. The stippled area represents that part of the striate cortex which faces posteriorly or postero-medially.

ponding area on the opposite side. It should be emphasized both that the figure is diagrammatic and that the calcarine fissure is subject to considerable variation in shape and in site relative to the striate cortex.

As Fig. 1 shows, central vision is represented at the most posterior part of the striate area and occupies a very large area relative to the area of the visual field which it represents. The peripheral field is represented most anteriorly and occupies a relatively small area. The representation of central vision is greater than Fig. 1 at first glance suggests, for as the stippling indicates, that part of the striate cortex faces posteriorly or postero-medially and therefore is foreshortened when the hemisphere is seen either from the medial or the posterior aspect.

The horizontal meridian of the visual field is represented in the depths of the calcarine fissure and the upper and lower halves of the vertical meridian in the lower and upper margins respectively of the striate cortex.

The cases to be described are chosen to illustrate this anatomy and to add some details to it. The aspects of the cases mentioned in the text are those which are immediately relevant and case histories are given in the appendix. Eight cases are described individually and their anatomical significance discussed. They are then shown together (Fig. 11) to indicate how their respective sites of injury are related to the type of defect in the visual field. In addition other cases are described which illustrate various points of interest.

Central vision is represented at the posterior pole and lesions confined to this site on one side confirm this and throw light on the problem of unilateral or bilateral representation of central vision. Case 1 (Fig. 2) is that of a man who received a low occipital injury, whose centre, measured on the radiograph, is 3·1 cm. to the left of the midline. The dura was penetrated and the lateral sinus was involved, but the injury was slight, and the patient had no retrograde or post-traumatic amnesia. Two and a half months after injury he had a right upper paracentral quadrantic scotoma indicating destruction to the left lower occipital pole. The lesion is strictly unilateral and it has caused a dense scotoma reaching to the fixation point, that is, involving " macular " vision.

It is in small lesions such as this that bilateral representation of central vision, if it occurred, would most readily show itself. Cases such as Case 1 cannot be interpreted on the assumption that central vision is represented bilaterally and afford proof that it is only represented unilaterally.

If more peripheral vision is represented more anteriorly, an injury entering through one occipital pole and passing forward before crossing the midline will cause a paracentral scotoma on one side with a pericentral scotoma on the other. Case 2 (Fig. 3) is that of a man who received an occipital injury whose centre on the radiographs is 5·2 cm. above the occipital protuberance, and 2·2 cm. to the right of the midline. The upper half of the right occipital pole has been destroyed, giving a lower left paracentral quadrantic scotoma reaching to the fixation point, and the injury has continued forward

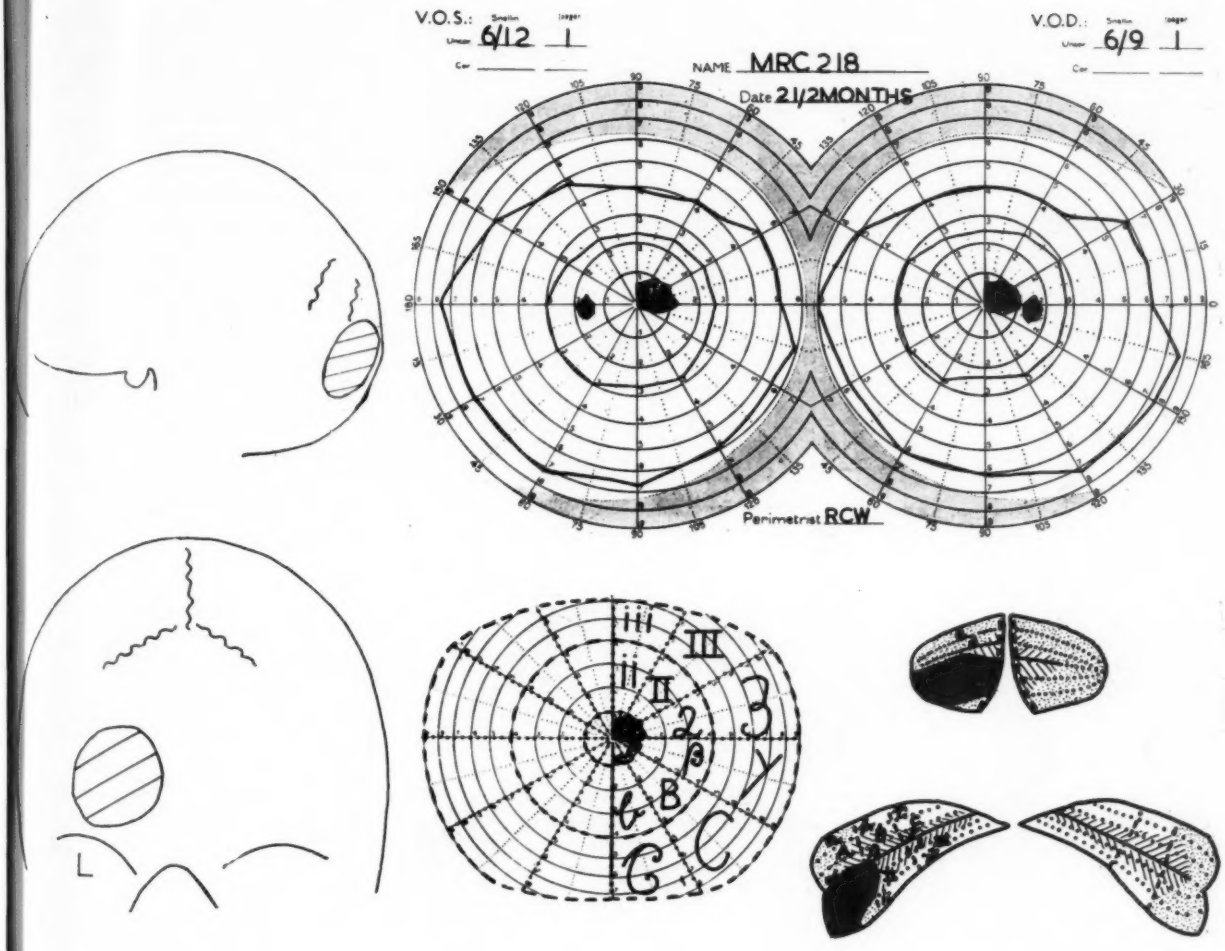


FIG. 2.—Low left occipital injury in Case 1 causing an upper right paracentral quadrantic scotoma to the fixation point. In this and subsequent figures a diagrammatic representation of the injury is shown using the same conventions as in Fig. 1.

to cross the midline and destroy the intermediate (that is, neither anterior nor posterior) part of the striate cortex on the left side, causing a partial arc scotoma in the lower right field at the periphery of the area of central vision. The sparing of the horizontal meridian on the right can be explained on the grounds that it is represented in the depths of the calcarine fissure and the injury did not penetrate so far.

Case 2 illustrates once more that central vision is represented unilaterally and shows that more peripheral vision is represented more anteriorly. It also suggests that the horizontal meridian is represented in the depth of the calcarine fissure.

Sparing of the horizontal meridian due to its representation in the depths of the fissure is more clearly illustrated in cases which suffered extensive damage confined to the medial surface of the striate cortex. Case 3 is of this type (Fig. 4). A series of foreign bodies has entered through a wound whose centre on the radiographs is 1·7 cm. above the occipital protuberance and only 0·8 cm. to the right of the midline. Four of these have destroyed the right occipital lobe causing a complete left homonymous hemianopia. A large foreign body has passed forwards and upwards crossing the midline by a very narrow margin. The field defect corresponds exactly with the radiographic appearances. For there is a deep " cove " extending from the vertical meridian (lower border of striate cortex) into the right upper quadrant about 10° above the fixation point, indicating that the missile has nicked the lower lip of the left calcarine fissure. In the lower quadrant there is a very much larger

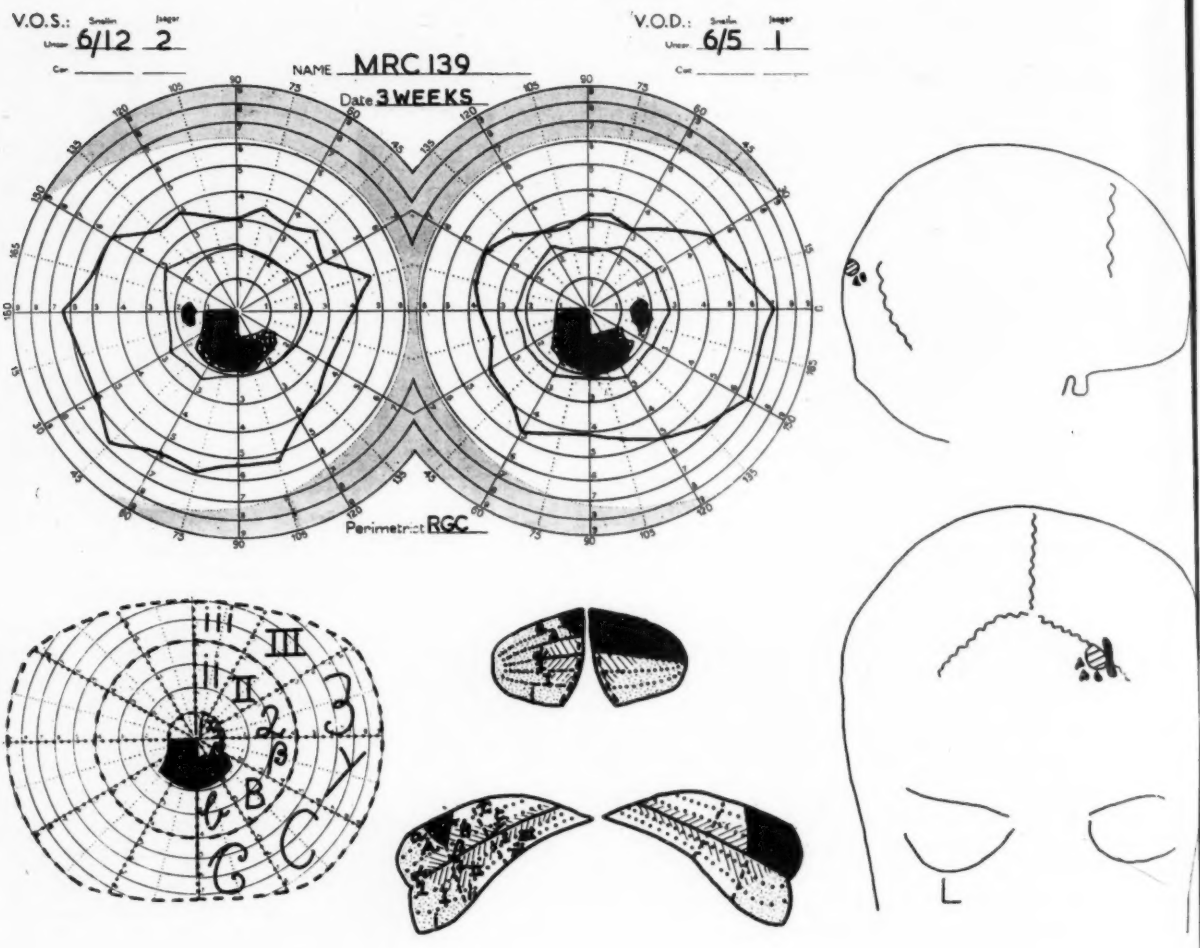


FIG. 3.—Right occipital injury in Case 2 causing a left lower paracentral quadrantic scotoma, and a right lower pericentral partial ring scotoma which is attributable to the injury passing forwards and across the midline.

cove indicating that damage to the upper lip has been much more extensive than to the lower and that the missile in its passage forwards and upwards has passed through the intermediate part of the upper striate cortex leaving its upper border before reaching the anterior end and so leaving extreme peripheral vision, that is, the area of monocular vision, intact.

Case 3 indicates that the horizontal meridian is represented in the depths of the calcarine fissure. Moreover it is clear that in the vertical meridian at least 5° of the visual field above and below the fixation point is represented in the walls of the calcarine fissure.

A midline injury may miss both occipital poles since these lie 1·5–2·0 cm. lateral to the midline, and injure both striate cortices where they reach the medial surface of the hemisphere and are separated only by the falx cerebri. Case 4 (Fig. 5) received a midline injury whose centre on the radiograph is 5·8 cm. above the occipital protuberance. The injury apparently first affected the right upper part of the striate cortex and travelled forward to cross the midline and cause more extensive damage to the left upper part of the striate cortex. The fact that the scotoma is very much larger on the right than on the left, though it is more peripheral (anterior), suggests that the missile did not entirely pass through the right striate cortex to reach the left, but must have traversed the interval between the two occipital poles.

It is reasonable to conclude from Case 4 that the point at which the two striate cortices reach the medial surface of the hemisphere represents a part

of the visual field not less than 5° from the fixation point in the vertical meridian. It may be argued that the injury reached the striate cortex from above instead of passing between the occipital poles. However, as Fig. 11 shows, the injury was less far above the level of the calcarine fissure than the occipital protuberance is below it, and therefore the injury may reasonably be supposed to be at the level of the upper border of the striate cortex.

The injury in Case 4 was quite considerable, and Case 5 (Fig. 6) suffered a very much smaller lesion. The tracing of the radiograph shows a foreign body lying in the skull defect with a piece of indriven bone immediately within the skull. The site of entry was on the right but the injury crossed the midline. It mainly involved the posterior fossa, and the report on the operation 17 hours after injury states that the torcula was also penetrated, but, fortunately for the patient, had become occluded with debris. Three weeks after he was wounded the visual fields were examined, although the patient made no complaints about his vision, and a small bilateral scotoma was found in the upper half field 8–10° from the fixation point involving the vertical but sparing the horizontal meridians.

This man (Case 5) suffered a minimal injury at the point where the striate cortex reaches the medial surface of the hemisphere, and indicates that this part of the striate cortex represents vision about 10° from the fixation point and therefore provides information about the area of striate cortex devoted to central vision.

A very small single lesion can involve both lower lips of the calcarine fissure at the point where the striate cortex reaches the medial surface of the hemisphere. Case 6 (Fig. 7) shows an example of this. A wound centred on radiographs 4·2 cm. above the occipital protuberance and 2·2 cm. to

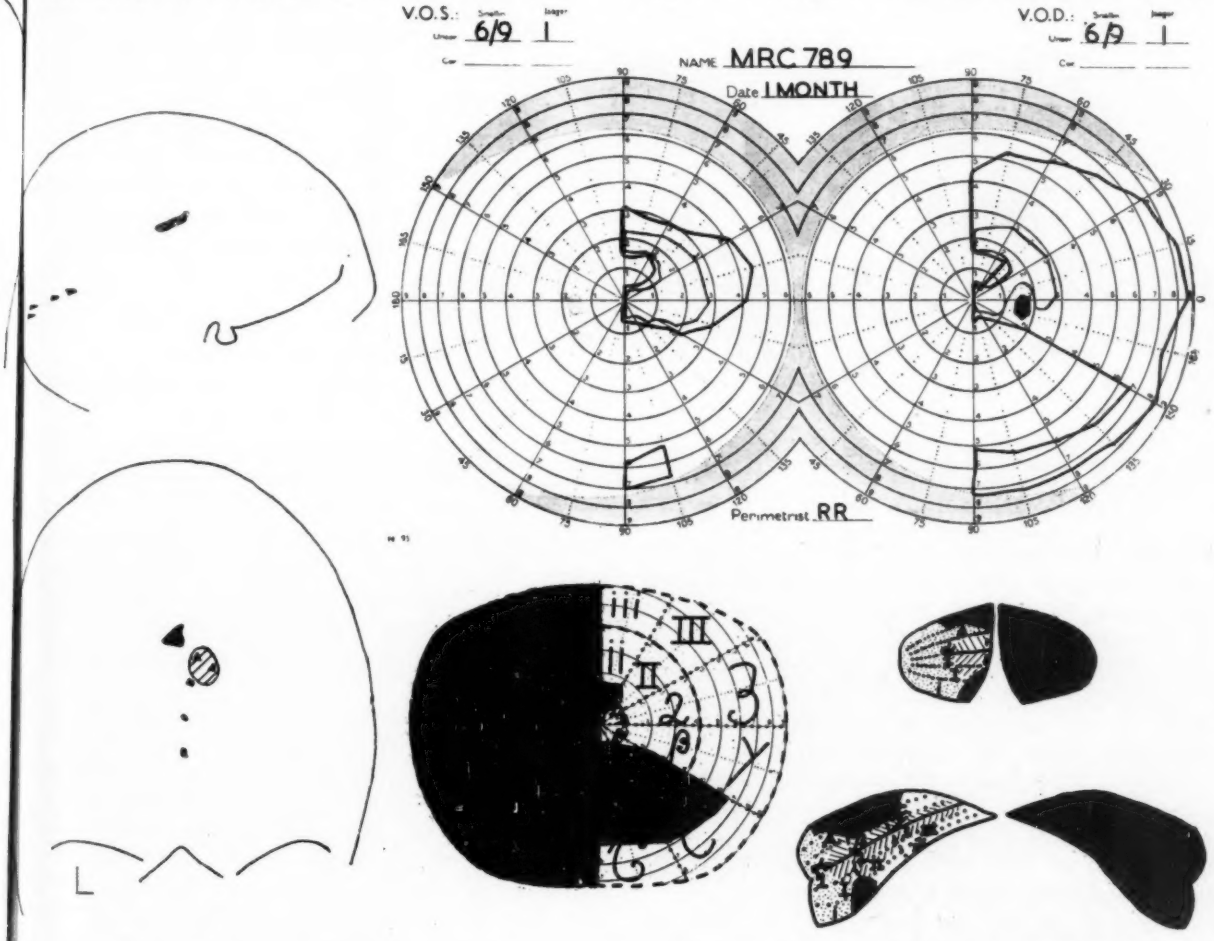


FIG. 4.—Right occipital wound in Case 3 causing left homonymous hemianopia. The large foreign body has just crossed the midline and damaged the medial surface of the left hemisphere. The horizontal meridian of the visual field represented in the depths of the calcarine fissure (hatched in the diagram) is spared.

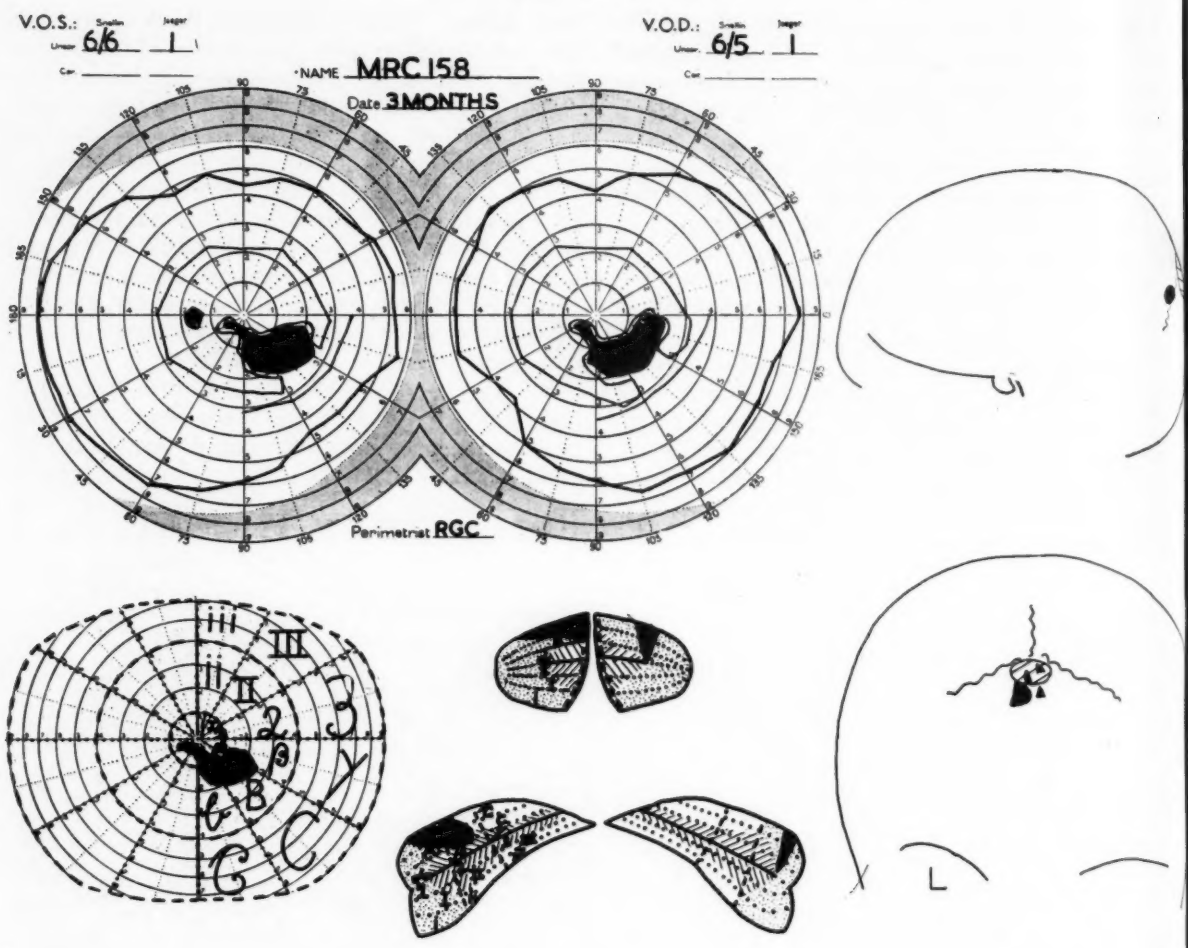
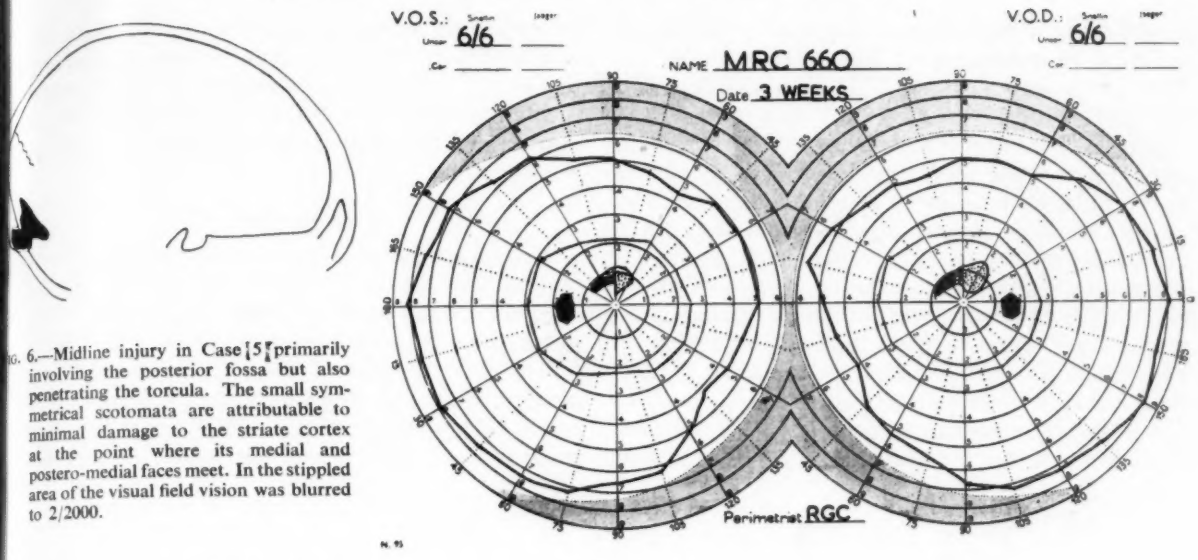


FIG. 5.—Midline occipital injury in Case 4 in which the most central vision has escaped. The scotoma on the right is the larger, though it is the more peripheral (more anterior lesion) suggesting that the injury passed partly through the space between the two occipital poles.

the right has destroyed a considerable part of the upper half of the posterior pole causing a left lower quadrantic paracentral scotoma reaching to the fixation point. This scotoma crosses the vertical meridian into the right lower quadrant indicating that the injury also crossed the midline. The two small circular scotomata in the upper half of the field indicate that the injury has also travelled to a minimal extent below the calcarine fissure and damaged the lower lips of the calcarine fissure on each side as described above. In this way a visual field which at first sight appears bizarre can be understood as the result of a single lesion.

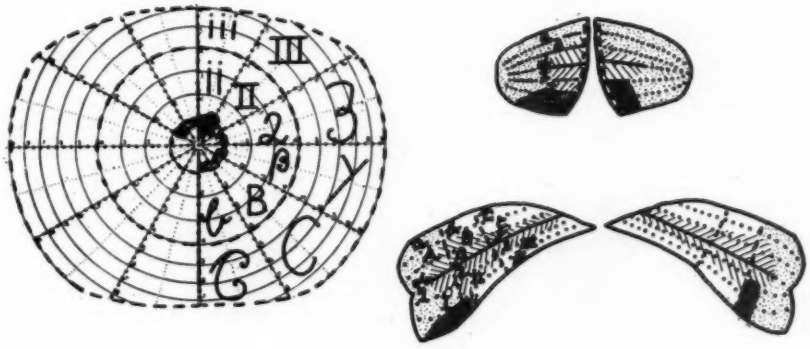
Case 6 shows that the lower lip of the calcarine fissure at the most posterior part of the striate cortex, which lies on the medial surface of the hemisphere, represents that part of the visual field which lies 8° to 10° from the fixation point along a radius 30° from the vertical. Moreover the existence of small dense scotomata provides clinical evidence that in man as in animals the retina is represented in the striate cortex in a precise point-to-point manner.

Most of the injuries considered above involve only small parts of the striate cortex. A more severe injury may destroy a great part of it on one or both sides. The cases of unilateral hemianopia, of which there are 54 in this material, will not be considered here in detail, but the relatively rare altitudinal hemianopia are of some interest. Case 7 (Fig. 8) received an extensive midline injury whose centre is 8·2 cm. above the occipital protuberance. Eleven months later he had an almost complete inferior altitudinal hemianopia.



ig. 6.—Midline injury in Case 5 primarily involving the posterior fossa but also penetrating the torcula. The small symmetrical scotomata are attributable to minimal damage to the striate cortex at the point where its medial and postero-medial faces meet. In the stippled area of the visual field vision was blurred to 2/2000.

The upper half of the striate cortex was destroyed or damaged severely enough to prevent it functioning, and this lesion is characteristic of extensive midline injuries in this situation, for they damage the whole antero-posterior length of the striate cortex from above.



Superior altitudinal hemianopia is much less common than the inferior variety. Case 8 (Fig. 9) has a field defect of this type due to a right occipito-temporo-parietal injury with a foreign body passing across the midline to reach the inner table of the skull on the left at about the same position as the site of entry. The position of the ventricle as determined by pneumoencephalography is shown in Fig. 9, and it is plain that the foreign body passed below the posterior horn of the ventricle, that is, directly through the lower half of the striate cortex on both sides.

This type of injury, the occipito-temporo-parietal wound with a foreign body passing horizontally across the midline, is characteristic of penetrating injuries causing superior altitudinal hemianopia. Cases with large midline injuries are not seen with this field defect, for such an injury will necessarily damage very severely the torcula and the great venous sinuses that drain into it and the victim does not reach hospital alive.

Total destruction of the striate cortex is so severe an injury that patients rarely survive it. Very few cases have been reported (see Brouwer, 1934), and, unless stringent precautions are taken in excluding the presence of perception of light, it is often open to doubt in reported cases whether the whole striate cortex is involved. Case 9 (Figs. 10 and 11) received a through and through bilateral parieto-occipital wound, and six months after the injury he had barely perception of light.

Extensive occipital wounds over the striate cortex are almost always fatal due to extensive damage to the venous sinuses. Complete or almost complete destruction of the striate cortex is therefore generally due to a parieto-occipital injury with a foreign body crossing the midline to reach a similar position on the opposite side. Case 9 is a typical example of this rare injury.

Cases 1 to 9 give a survey of the various defects in the visual field due to penetrating occipital wounds, and Fig. 11 shows the site of injury in these nine cases plotted on a single skull outline by the measurement from the radiographs. The skull outline was

traced from a half axial radiograph in which the occipital protuberance is just visible above the floor of the anterior fossa. The figure shows that the sites of injury correspond well with one another, and so confirm the interpretations which were put upon them when they were described above. It also enables an estimate to be made of the position of the calcarine fissure which is indicated by a dotted line in Fig. 11. It is nearly 3 cm. above the occipital protuberance. The wound of Case 9 (Fig. 10), who was virtually blind, passed right through this region, whereas that of Case 8 (Fig. 9), who had a superior altitudinal hemianopia, passed from one side to another directly below it.

The evidence presented above confirms the view of Holmes on the representation of the visual field in the striate cortex and amplifies it as regards the extent of the posterior striate cortex which is devoted to central vision. It indicates that central vision (including " macular " vision) is represented strictly unilaterally, and that representation is of a sharp, point-to-point character.

Discussion

This investigation is based on a series of 72 cases of injury to the striate cortex by wounds, mainly gunshot, which penetrated the dura mater. This material is in accord with Holmes and Lister's (1916) view that central vision is represented most posteriorly in the striate cortex ; that serial concentric zones of the visual field from the fixation point to the periphery are represented in this order

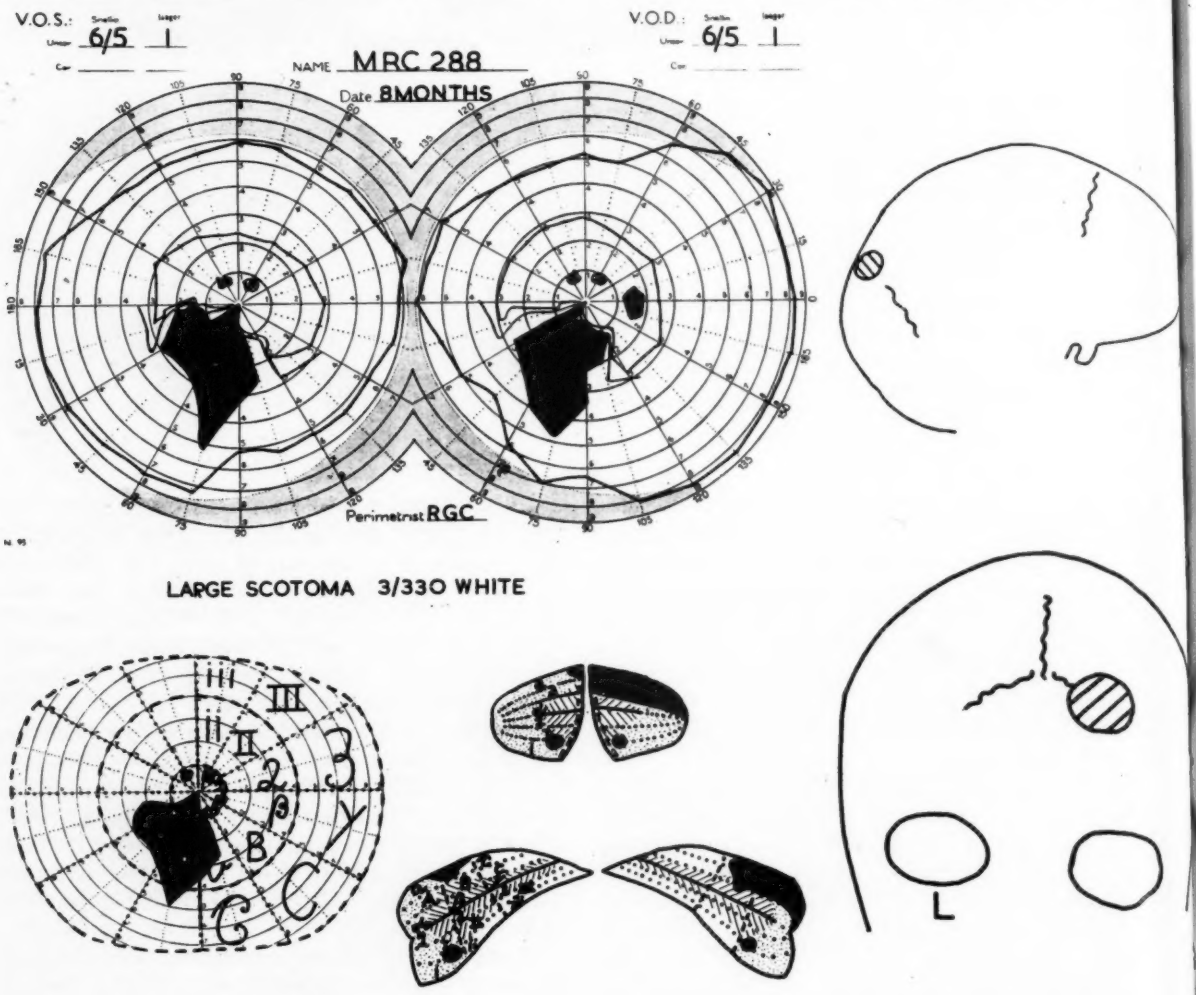


FIG. 7.—Right occipital injury in Case 6 with extensive damage to the right occipital pole causing a left lower paracentral scotoma. The two small symmetrical scotomata in the upper field are attributable to involvement of the lower lips of the calcarine fissure at the point where the medial and postero-medial faces of the striate cortex meet. Since the hatched area in the diagram represents the walls of the calcarine fissure pulled apart, the lesion is single.

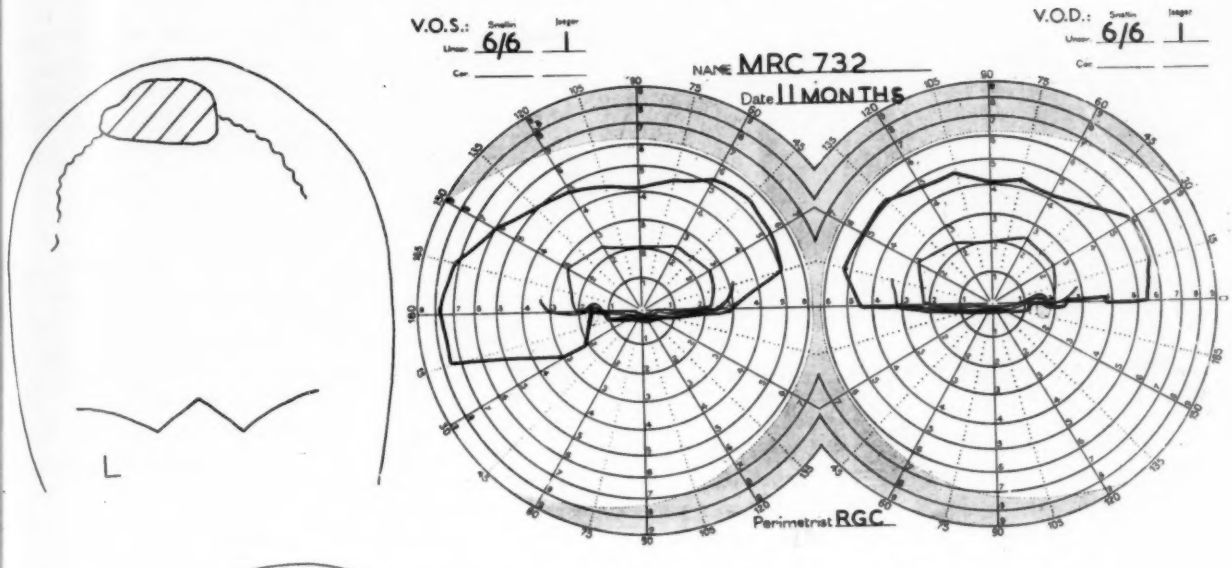


FIG. 8.—Extensive midline high occipital injury in Case 7 causing inferior altitudinal hemianopia.

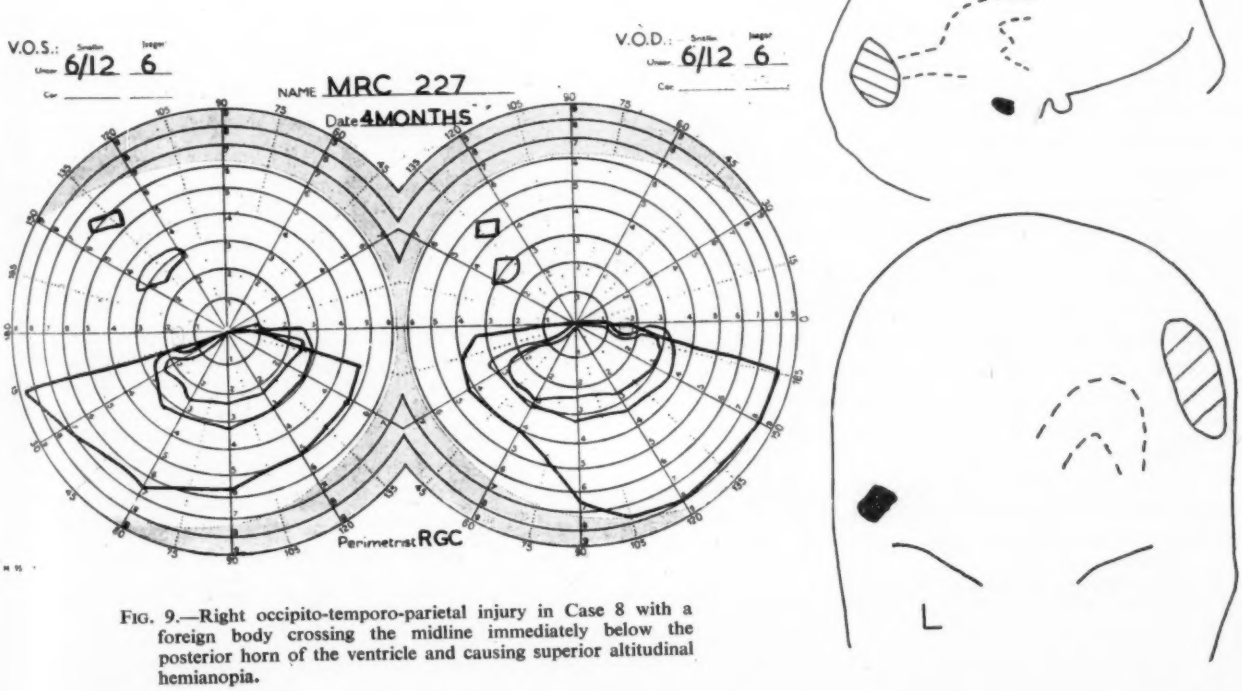


FIG. 9.—Right occipito-temporo-parietal injury in Case 8 with a foreign body crossing the midline immediately below the posterior horn of the ventricle and causing superior altitudinal hemianopia.

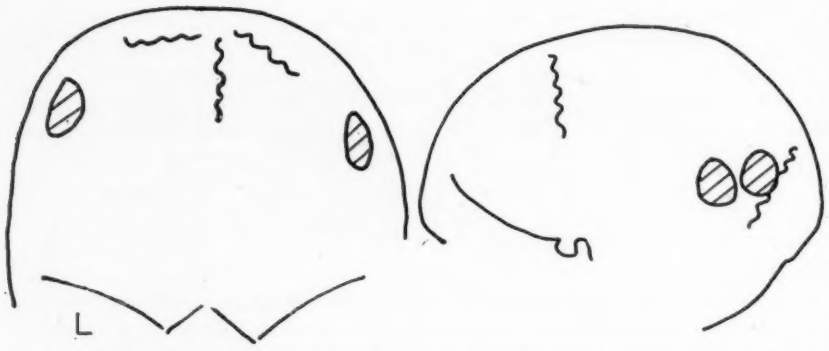


FIG. 10.—Through and through bilateral parieto-occipital injury in Case 9 causing almost complete blindness.

from behind forward ; and that the lower half field is represented in the upper half of the striate cortex and vice versa. It also throws new light on some debatable problems and makes it possible to localize certain parts of the visual field on the striate cortex in greater detail than before.

" Macular " Representation.—The thesis that the " macula "—which seems to vary considerably in size from one author to another and is rarely defined*—is represented bilaterally is based solely on the alleged observation that in occipital lobe lesions, but not in lesions of the anterior radiation, there is " macula sparing ". This observation is, however, open to considerable doubt, for Allen (1930) in a review of a large series of tumours involving the occipital lobe from the National Hospital, London, found that there was hemianopia splitting the macula in 32·5%. Horrax and Putnam (1932) from Cushing's clinic reviewed another large series of occipital tumours, including only those strictly confined to the occipital lobe, and found that 12·5% had hemianopia splitting the macula. These two figures do not agree well and have been brought forward as evidence in favour of bilateral representation of the macula. Horrax and Putnam, however, did not draw this conclusion and it is difficult to see how one can. For in tumour material it is never possible to say that all the visual cortex has been rendered functionless, and Horrax and Putnam's stricter criteria may well account for the difference by excluding all the large tumours which are more likely to destroy the whole visual pathway. And in any case there remains to be explained the fact that in at least 12·5% the hemianopia split the macula. Moreover Bender and Kanzer (1939) found that there was no correlation between preservation or splitting of the macula and the site of the lesion in the radiation or striate cortex, and Austin, Lewey, and Grant (1949) found the sparing of central vision was no greater in cases after occipital lobectomy than in those with chiasmal lesions.

The crucial experiment in this controversy is to determine whether a small lesion of one occipital lobe can produce a field defect reaching to the fixation point. It is impossible to decide this point by experiments on animals, and it is essential that the lesion must be small because large lesions such as occipital lobectomy have given contradictory results (Halstead, Walker, Bucy, 1940), possibly owing to the severity of the visual disability which the patients suffer. The cases (Nos. 1 and 2) reported above (Figs. 2, 3) are accidental experiments of this type of which there are many other examples in this material and in the literature (Holmes and Lister, 1916 ; Greear and McGavic, 1946 ; Symonds, 1945), and they show that in small lesions of the occipital pole the scotoma reaches to the fixation point.

Two objections to these cases may be raised. First it may be said that without microscopic examination of the brain it is impossible to say exactly how extensive each lesion was. Although there is some truth in this, it does not affect the argument since for the present purposes all we have to be sure of is that the injury affected one occipital pole but not the other. The slightness of the injury is indicated by the absence of retrograde or post-traumatic amnesia and by the report on the operation. It is unlikely that an injury such as these would cause more than local damage, but if it involved the opposite occipital pole, there would be unmistakable evidence of it in a scotoma in the opposite half field.

The second objection that may be raised is that the visual fields are inaccurately charted. This is always a possible reply to unwelcome evidence, but to make it valid it is desirable to show how the inaccuracy could have crept in. In these cases the observations were made on a Bjerrum screen by trained observers who were constantly doing such tests, but who had no preconceived ideas about what they " ought " to find. The scotomata are small and dense (20/2000) and have well-defined borders, that is, they are of a type that is particularly easy to chart accurately when once they have

* Putnam and Liebman (1942) however state that the macula subtends an angle of 9°, the fovea centralis an angle of 2°.

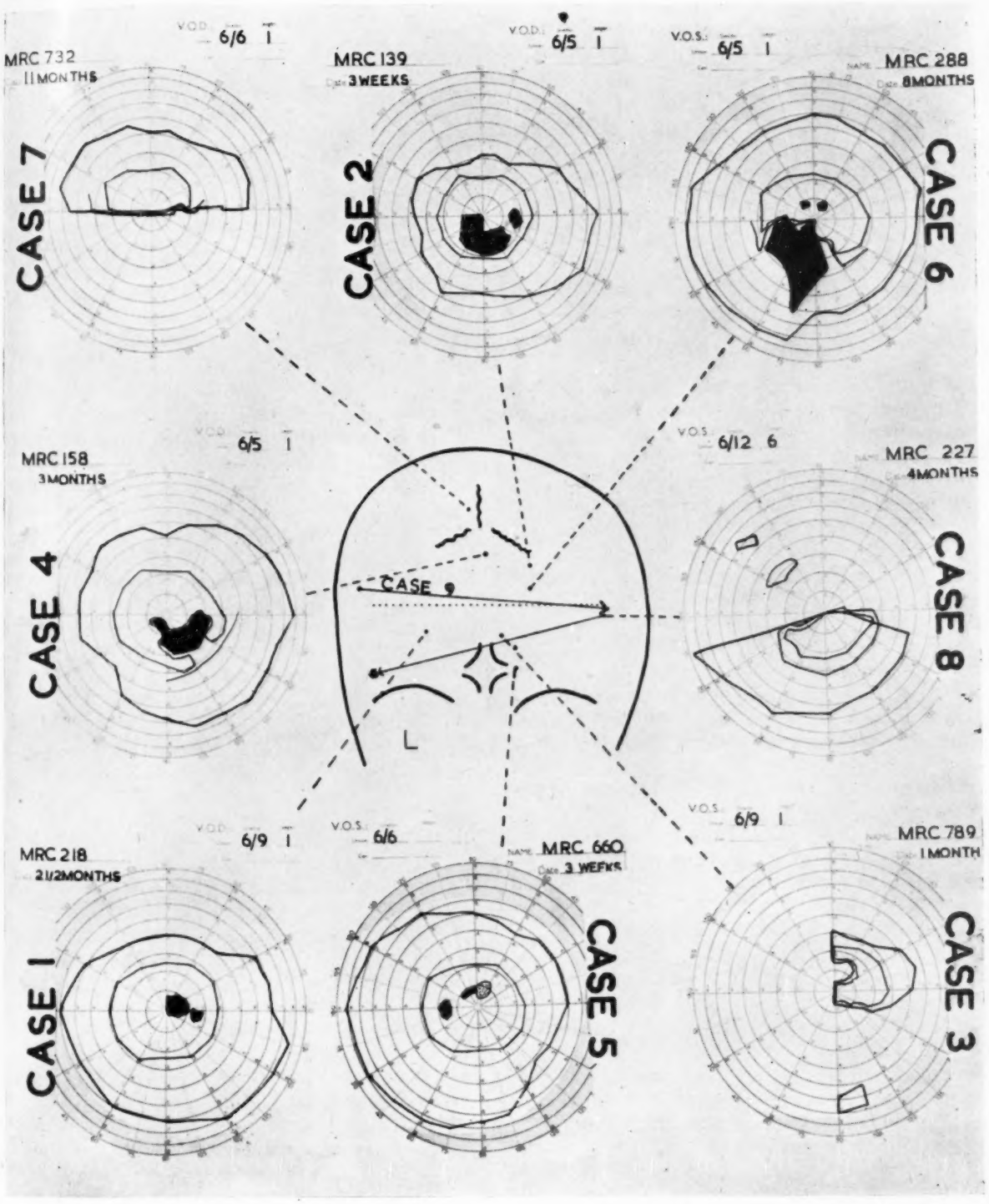


FIG. 11.—The sites of injury in Cases 1 to 9 plotted by measurement on the radiographs from the occipital protruberance. The dotted line indicates the approximate level of the calcarine fissure.

been detected. The patient was watched to see that fixation was well maintained, and though a patient may alter his fixation to bring a scotoma further from the fixation point, it is hardly credible that he should alter it to bring the scotoma towards the fixation point.

We are therefore justified in accepting the evidence that a partial lesion of one occipital pole will produce a scotoma reaching to the fixation point, and therefore we must conclude that the " macula " is represented strictly unilaterally. Holmes and Lister (1916) and Lister and Holmes (1916) reached the same conclusion from their experience in the first world war, as did Greear and McGavic (1946) in the second world war, and Putnam and Liebman (1942) from an extensive review of the literature. The advocates of bilateral representation of the " macula " postulate a tract from one lateral geniculate body to the opposite striate cortex crossing the midline in the corpus callosum, but Putnam and Liebman conclude that on the one hand there is no good evidence to show that such a tract exists and on the other there is a great deal of evidence that it does not. The subject of bilateral representation of the macula has only been discussed here again because belief in it appears not yet to be dead.

The apparent sparing of central vision which may occur in cases of hemianopia has been explained by Bender and Kanzer (1939). Tumours and certain types of injury often do not involve the visual pathways directly but may damage them diffusely either by oedema, by interference with blood supply, or by anatomical distortion due to an expanding lesion. In such cases the visual acuity in the affected half field is depressed, and in extreme cases the only part of the field where appreciable vision is retained is that part where visual acuity is normally the highest, namely around the fixation point. In cases of tumour it is impossible to be sure in any given case whether this mechanism is not responsible for macula sparing. Cases in which the occipital lobe has been destroyed may also show sparing of central vision, but, as Bender and Kanzer have shown, the sparing is not confined to central vision, and on careful testing the whole dividing line between the normal and blind half fields can be shown to be slightly to the affected side of the fixation point. In these cases the patient learns to use a pseudo-fovea as the fixation point. This mechanism, which is analogous to that commonly used by sailors who wish to see faint lights at night, was spontaneously described by a hemianopic patient from this series of head injuries who said that each time he fixed on an object he saw only half of it and automatically shifted his gaze to include as much of it as possible. Undoubtedly many such patients employ the same mechanism unconsciously.

It has been suggested that cerebral vision is represented not only in the posterior part of the striate cortex but also more anteriorly (Brouwer, 1934 ; German and Fox, 1934 ; Penfield and Evans, 1934). Case 1, in which a very slight occipital injury caused a dense paracentral quadrantic scotoma to the fixation point, is strong evidence against any representation of central vision in the anterior part of the striate cortex. Brouwer, on the strength of experiments on monkeys supported by some clinico-pathological evidence, believed that in the cortex " the macula area reaches further frontal, becoming smaller between the dorsal and ventral parts of the retina ". The cases just mentioned are evidence against this. Moreover, if Brouwer's view were correct we would find that when a vertical lesion has occurred through part of the striate cortex the field defect would encroach on the macula near the horizontal meridian, but in Case 4 (Fig. 5) in which a lesion of this nature presumably occurred on the left side, the resulting scotoma is an arc reaching from the vertical almost to the horizontal meridians. This conforms to Holmes and Lister's view (1916a) that serial concentric zones of the retina from the macula to the periphery are represented in this order from behind forwards in the visual area.

Representation of Horizontal Meridian.—Henschen (1911) was the first to suggest on the basis of a single case studied clinically and pathologically that the horizontal meridian was represented in the depths of the calcarine fissure. Holmes (1918) independently reached the same conclusion from his studies of head injuries in the first world war, and in 1931 reported a case of cerebral vascular anomaly studied clinically and pathologically which supported this view. In the first world war radiography was not readily available and the site and track of intracranial foreign bodies were therefore open to some doubt. In the civilian cases, though necropsy demonstrated the site of the lesion, the examination of the visual field was done during the course of the patient's last illness shortly after a cerebral vascular accident, conditions which make accurate examination of the visual fields difficult. In the present material this suggestion that the horizontal meridian is represented in the floor of the calcarine fissure offers an explanation of the frequent sparing of the horizontal meridian with involvement of the vertical meridian in lesions of

the medial surface of the hemisphere (Cases 2 and 5, Figs. 3, 6). More important, however, is Case 3 (Fig. 4). The radiograph shows that a foreign body must have skimmed the medial surface of the left striate cortex, and the visual fields were examined four weeks after injury when the patient was fit to cooperate well. The field defect with sparing of the horizontal meridian confirms the view that the horizontal meridian is represented in the floor of the calcarine fissure.

Extent of the Representation of Central Vision.—It is generally agreed that in the striate cortex central vision obtains a very large representation compared to peripheral vision, but there is little evidence to indicate just how large it is or to localize accurately in the striate cortex any part of the central or pericentral visual field. The present material gives some help in this problem.

In Case 3 (Fig. 4) an injury which destroyed the right striate cortex also involved some of the left striate cortex where it lies on the medial surface of the hemisphere. In the right upper quadrant of the visual field there is a small semicircular defect running in from the vertical meridian and extending from about 5° to 15° from the fixation point. It is reasonable to suppose that this is due to an injury to the lower lip of the calcarine fissure and the striate cortex inferior to it near the point where the striate cortex passes from the occipital pole to the medial aspect of the hemisphere, and therefore we may provisionally localize this area of the visual field in this part of the striate cortex.

Cases 5 and 6 (Figs. 6, 7) confirm this suggestion and make the localization more accurate. In Case 5 there was a midline injury principally involving the posterior fossa. The very small scotomata, of which the patient was unaware (Fig. 6), represent minimal injury to both striate cortices at the most posterior point where the two are in apposition. An injury in this situation due to a wound from below would extend up from the inferior border of the striate cortex and if of minimal severity would spare the calcarine fissure; in accordance with expectation the scotomata extend from the vertical meridian around the 8° arc and spare the horizontal meridian. In Case 6 there was a considerable injury to the right occipital pole. The two small scotomata in the upper half of the field at first sight appear bizarre, but are readily explicable as the result of an injury coming from above and behind and just reaching the lower half of the striate cortices to involve to a minimal degree the lower lips of the calcarine fissure at the most posterior point where the two striate cortices are in apposition. In this way they can be interpreted as the result of a single lesion. As the cases presented above lead us to expect, the scotomata lie 8° from the fixation point. The two scotomata lie on the radii 30° from the vertical meridian, and this suggests that at least in this part of the visual field the walls and floor of the calcarine fissure represent two thirds of the visual field above and below the horizontal meridian.

Summary

A series of 958 cases of penetrating head injury, mainly gunshot wounds, has been reviewed to determine what light they throw on the anatomy of the striate cortex (area 17). In 188 of these there was a visual field defect attributable to injury to the visual radiation or striate cortex. In 72 cases the injury primarily affected the striate cortex, and of these characteristic examples are presented and their anatomical significance discussed.

Central (" macular ") vision is represented unilaterally.

The horizontal meridian of the visual field is represented in the floor of the calcarine fissure.

The extent of striate cortex devoted to central vision is defined. Central vision within the 8° to 10° circumference (i.e. macula vision) is represented on that part of the striate cortex which faces posteriorly or postero-medially. The remainder which faces medially represents vision more peripheral than 10° from the fixation point.

The lips of the calcarine fissure at the point where the striate cortex on the medial surface of the hemisphere becomes continuous with that on the postero-medial surface represents the points 8° from the fixation point and 30° from the vertical meridian.

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We much regret an error in Fig. 8 of Part I (p. 103). Fig. 8 comprises the three line drawings only marked (*a*), (*b*), and (*c*).

APPENDIX

Case 1.—M.R.C. 218,* a man aged 19, on August 7, 1944, received a gunshot wound in the left occipital region 3·1 cm. from the midline and through the upper margin of the transverse sinus (Figs. 2 and 11). He did not lose consciousness and had no retrograde or post-traumatic amnesia. He was blind for about 10 minutes, and when seen at a mobile neurosurgical unit 18 hours after injury there was a right homonymous hemianopia and a slight right facial weakness. At operation 56 hours after injury the lateral sinus was found to have been almost completely torn across by a metallic foreign body which was lying partly outside the dura. Debris was removed from a cavity the size of a small plum, exposing the tentorium.

On arrival at the Military Hospital for Head Injuries, Oxford, five days after injury no abnormal physical signs were detected clinically but full examination of the visual fields revealed a right paracentral scotoma reaching to fixation point and about 10° out from it. It involved the right upper and part of the right lower quadrant. Two months after injury the visual field remained almost unchanged except that the lower quadrant was involved to a smaller extent (Fig. 2).

Case 2.—M.R.C. 139, a man aged 30, on July 21, 1944, received an occipital gunshot wound whose centre was 5·2 cm. above the occipital protuberance and 2·2 cm. to the right of the midline (Figs. 3 and 11). He was momentarily unconscious and all limbs were paralysed for a few minutes.

On admission to the Hospital for Head Injuries two days after the injury he was rational and fully orientated, and no abnormal physical signs were detected clinically. At operation 64 hours after injury a defect in the dura was found measuring 1·5 × 0·73 cm. and a funnel-shaped track led in from it from which debris was removed to a depth of nearly 2 cm. His convalescence was delayed by meningeal infection lasting a week but three weeks after injury he was free of symptoms and the only abnormality was in the visual fields. They showed a left lower quadrantic paracentral scotoma continuous with a right lower pericentral partial ring scotoma (Fig. 3).

Case 3.—M.R.C. 789, a man aged 30, on April 15, 1945, received a gunshot wound in the right occipital region whose centre was 1·7 cm. above the occipital protuberance and 0·8 cm. from the midline (Figs. 4 and 11). He had a retrograde amnesia of about an hour and a post-traumatic amnesia of five or six days. Thirty-four hours after injury the wound was debrided but the track was not followed deeply.

On admission to the Hospital for Head Injuries five days after injury he was moderately confused and grossly disorientated in time, but there was no dysphasia. The left pupil was larger than the right. His ability to appreciate the direction of passive movement of the digits of all limbs was impaired but other modalities of sensation were normal, and there was no astereognosis or finger agnosia. There was no weakness and no reflex abnormalities.

He made a good recovery and three months after injury the only abnormality on physical examination, apart from the field defect, was moderate disturbance of joint sense in the fingers of the right hand.

Five days after injury he was thought on confrontation to have vision only in the right upper quadrant of both eyes. Four weeks after injury the visual fields showed a complete left homonymous hemianopia with a small "cove" penetrating from the vertical meridian into the right upper quadrant about 8° from the fixation point, and a very much larger cove involving a large part of the lower quadrant and bounded in part only by the area of monocular vision (Fig. 4).

Case 4.—M.R.C. 158, a man aged 24, on May 23, 1944, received a gunshot wound in the midline 5·8 cm. above the occipital protuberance (Figs. 5 and 11). There was no retrograde amnesia and post-traumatic amnesia was less than an hour. At operation the following day the wound was found to have penetrated the sagittal sinus which bled very freely. Superficial debris was removed but full exploration of the extent of the wound was not possible owing to difficulty in controlling the bleeding from the sagittal sinus.

Seven days after injury he was thought to have an inferior altitudinal field defect. When admitted to the Hospital for Head Injuries two and a half months after injury the only abnormality on physical examination was in the visual fields, in which there was a large right lower quadrantic paracentral scotoma and very much smaller left lower paracentral scotoma (Fig. 5).

Case 5.—M.R.C. 660, a man aged 29, on February 27, 1945, received an occipital gunshot wound. There was no retrograde amnesia and post-traumatic amnesia lasted half an hour. At operation 17 hours after injury the site of entry was found to be in the posterior fossa immediately to the right of the midline, but an indriven bone fragment (Figs. 6 and 11) had penetrated the torcula, bleeding from which had fortunately been checked by debris.

On admission to the Hospital for Head Injuries three days after injury he was alert and well orientated, and no abnormalities were detected on clinical examination. He made no complaints about his vision, but examination

* Reference number of the M.R.C. Penetrating Head Injury File, Military Hospital, Wheatley, Oxford.

of the visual fields three weeks after injury showed that he had a small bilateral scotoma, complete on the left, incomplete on the right, in the upper half field 8–10° from the fixation point and involving the vertical but not the horizontal meridian. The scotoma was unchanged seven weeks after injury.

Case 6.—M.R.C. 288, a man aged 22, on September 10, 1944, received a gunshot wound centred 4·2 cm. above the occipital protuberance and 2·2 cm. to the right of the midline (Figs. 7 and 11). There was neither retrograde nor post-traumatic amnesia, but for 10 minutes the whole of his vision was very indistinct.

On admission to the Military Hospital for Head Injuries two days later he was rational and well-orientated, and to confrontation was found to have a defect in the left lower quadrant of the visual field. There were no other abnormal physical signs. At operation 66 hours after injury a dural tear was found measuring 1·5 × 0·5 cm. and debris was removed from the track to a depth of 1·5 cm.

Ten days after injury the fields were charted in bed and the left lower quadrantic defect was found to extend also into the right lower quadrant. One month after injury the visual fields were first fully tested and were identical with those eight months after injury (Fig. 7). There was a large left lower paracentral scotoma extending also into the right lower quadrant and a small scotoma in each upper quadrant about 8° from the fixation point and 30° from the vertical meridian.

Case 7.—M.R.C. 732, a man aged 23, on May 12, 1944, received an extensive midline gunshot wound whose centre was 8·2 cm. above the occipital protuberance (Figs. 8 and 11). There was no retrograde amnesia and the post-traumatic amnesia was about 10 days.

On admission to the Hospital for Head Injuries 11 months after injury he had an inferior altitudinal hemianopia (Fig. 8) and no other abnormal physical signs except slight increase in the reflexes of the left upper limb.

Case 8.—M.R.C. 227, a man aged 23, on May 13, 1944, received a gunshot wound in the right occipito-temporo-parietal region and a metallic foreign body passed across the midline immediately below the posterior horns of the ventricles and came to rest in the left temporo-parietal region (Figs. 9 and 11). He had no retrograde amnesia, was unconscious for half an hour, and had a post-traumatic amnesia of three days during which there were a few episodes which he remembers. The wound was debrided about 18 hours after injury, when sight began to return.

On admission to the Hospital for Head Injuries three months after injury there were no abnormal physical signs except for an upper altitudinal hemianopia which remained unchanged during the next five weeks (Fig. 9). As this involved central vision he had great difficulty in reading for he had to scan words up and down.

Case 9.—M.R.C. 851, a man aged 23, on January 29, 1945, received a through and through bilateral parieto-occipital wound (Figs. 10 and 11). His retrograde amnesia was two or three hours and post-traumatic amnesia about five weeks.

On admission to the Hospital for Head Injuries six months after injury the only abnormal physical signs were complete anosmia and virtually complete blindness, for he could barely distinguish light from darkness.

I wish to express my thanks to Dr. W. Ritchie Russell for his constant help and encouragement. I would also like to thank the surgeons and physicians of the Military Head Injuries Units, both at Oxford and in the field, for their detailed notes, and the orthoptists, in particular Miss Coates-White, D.B.O., for their help with the visual fields.

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DYSPHASIA IN LEFT-HANDED PATIENTS WITH UNILATERAL BRAIN LESIONS

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The importance of the left cerebral hemisphere for speech and allied functions in right-handed persons is an accredited fact, whatever may be its correct explanation. In the same way it has commonly been assumed that in the case of left-handed persons the same importance attaches to the right hemisphere. Thus unequivocal handedness, whether right or left, has been thought to imply a corresponding " dominance " of the hemisphere contralateral to the preferred hand.

Evidence concerning the cerebral organization of left-handed people has inevitably been scarce. One of the earliest cases on record is that reported by Hughlings Jackson (1879), of motor aphasia associated with left-sided hemiplegia in a railway signalman whose speech was restricted to the single recurring utterance, " Come on to me !" ; the patient was said to be left-handed. Later Head (1926) reported a case of semantic aphasia in a man who had always been strongly left-handed, " even using a chopper with the left hand " ; here again the lesion was right-sided. Exceptional cases have been reported from time to time in which aphasia was associated with a lesion of the hemisphere ipsilateral to the individual's preferred hand. Bramwell (1899) suggested that in most of these cases, which he termed " crossed " aphasia, enquiry will reveal first that the patient's ancestors were all right-handed, and secondly that the patient himself has been taught to write with the right hand and/or is ambidextrous. Crossed aphasia as a transitory phenomenon is not uncommon, and was in Bramwell's view due to the fact that in certain individuals corresponding areas of the minor hemisphere play a definite, if subordinate, part in speech, so that injury to such areas gives rise to mild and transient dysphasic symptoms. Persistent crossed aphasia, on the other hand, was in Bramwell's experience confined to left-handers, except where there was reason to suppose that the normal development of the speech centres had been interfered with in early life. It may be added that the present writers have searched the literature in vain for a convincing case of crossed aphasia in an overtly right-handed person.

The problem of ambidexterity and mixed hand dominance has seldom been considered from this point of view. Some writers have suggested that bilateral cortical representation of speech functions is to be expected in ambidextrous cases, as also in young children before unequivocal hand dominance has been finally established. Gowers (quoted by McNaughton-Jones, 1914), in his plea for the cultivation of ambidexterity, put forward the view that " as far as can be judged from present facts, by the use of both hands equally for all manual occupations, including writing, we should secure immunity from grave defects of speech " (i.e., if disease of either hemisphere were to occur). Such a view appears to have been founded on somewhat dubious theoretical considerations rather than on clinical and pathological evidence, which at that time was virtually non-existent. Admittedly Bastian (1898) had reported the case of an ambidextrous marine engineer who developed complete motor aphasia in association with right-sided hemiplegia. The patient continued to write fluently with his left hand, and before his illness had been able to use both hands equally well. Speech recovered suddenly 24 days after the onset of the attack. However, while doubtless the early literature of aphasia contains a few other unusual cases of this type, it is only comparatively recently that systematic study of the laterality of brain lesions causing aphasia in relation to handedness has been attempted. Thus Weisenburg and McBride (1935) found that among 92 cases of unequivocal handedness there were only four exceptions to the rule that aphasia results from a lesion of the dominant hemisphere as indicated by handedness, and fails to result from a lesion of the minor hemisphere ; in other words, the inference from handedness to cerebral dominance was justified in about 95% of their cases. Of their five ambidextrous cases, three

developed aphasia from a left-sided lesion and one from a right-sided lesion.

Chesher (1936) summarized the evidence from 166 cases of circumscribed lesion within the speech area of one or other cerebral hemisphere. He found that where a patient was strictly unilateral in his hand dominance, be it right or left, hemisphere dominance followed the normal rule. (There were, however, only three purely left-handed patients in his series.) Where on the other hand a naturally left-handed patient had been taught to write with the right hand, thus acquiring a measure of ambidexterity in some cases and a mixture of hand preferences in others, aphasia appeared with lesions of either hemisphere. In all there were nine such cases; all showed aphasic symptoms, the lesion being left-sided in five cases, right-sided in four. In regard to this atypical group Chesher suggested that "the tentative conclusion is justified that their language mechanism is unlateralized, so that a lesion on either side is capable of producing a disturbance of speech".

Needles (1942) quoted four cases in which the common factors were loss of function of the right hand, adoption of function by the left hand, and onset of aphasia at a much later date. The lesion giving rise to the aphasia was left-sided in two cases and right-sided in the other two. He adopted Chesher's hypothesis of bilateral cortical representation of speech in explanation of these cases, while at the same time suggesting that in naturally left-handed persons training of the right hand, for example, in writing, may result in the left hemisphere acquiring dominance for speech. An account by Tilney (1936) of the circumstances of his own aphasia is of interest in this connexion.

Conrad (1949) studied 47 cases of traumatic brain lesion in markedly left-handed patients. Of these 18 showed some form of speech disturbance, the lesion being left-sided in 10 cases, right-sided in seven, and bilateral in the one remaining case. Severe and lasting dysphasic syndromes were observed in five cases of left-sided and the same number of right-sided injuries; other left-handed cases showed only slight and transitory dysphasia where the nature of the injury was such as would have been expected to cause a more profound loss of speech. Thus left-handedness, in Conrad's view, differs from right-handedness in that it does not imply strict dominance of the contralateral hemisphere, but on the contrary shows all the signs of less advanced specialization.

In view of the limitations and inconclusiveness of the evidence produced by previous writers, it was felt that any fresh cases bearing on the problem of cerebral dominance should be placed on record. The authors were fortunate in having access to the detailed histories of approximately 1,150 cases of penetrating brain wounds from the recent world war. These were studied from the viewpoint of psychological functions in general, but especially with reference to handedness and the different effects of left- and right-sided cerebral lesions. In what follows we shall be concerned primarily with the various manifestations of dysphasia, although other symptoms will be noted as and when they are considered relevant.

Selection of Cases

Despite the large total of cases surveyed, the necessary information did not prove to be available in a sufficient number to enable a statistical study to be made, as was originally planned. (Left-handedness is, after all, a comparatively rare phenomenon, being confined in its more obvious forms to about 7 to 8% of the population, according to conservative estimates (Wile, 1934)). The only alternative was to select from the total material cases showing clear evidence of a marked tendency towards left-handedness and to report them in some detail. It was hoped that even a very small number of carefully studied cases might provide useful information concerning the degree of cerebral dominance associated with atypical handedness.

The selection of cases was based on the following criteria. (1) the lesion must be strictly unilateral. (2) The patient must have been tested specifically for dysphasia by adequate methods and at varying intervals. A psychological report based on routine psychometric tests, while clearly desirable, was not considered indispensable. (3) In the absence of dysphasia the lesion must be such as would be expected to interfere with speech functions if the affected hemisphere were the dominant one. (4) Adequate information was required as to the patient being left-handed; mere indications that the patient was not entirely right-handed were considered insufficient. (5) The patient should be of at least average pretraumatic intelligence, in so far as could be judged from his personal history and/or psychological tests. (In the event most of the patients selected were of above average intelligence.) This proviso was made in order to exclude cases of so-called "pathological" left-handedness, as described by Russell Brain (1945).

This method of selection yielded a total of no more than 10 cases, in five of which the lesion was left-sided and in five right-sided. All showed some degree of dysphasia in the early stages of recovery, and all were predominantly left-handed.

It must be emphasized that, with one or two exceptions, the writers were unable to examine these cases personally, and were thus obliged to rely on the written testimony of other observers and, in some cases, of the patients themselves.

Cases of Left Hemisphere Injury

The severity of the dysphasic symptoms, both initial and residual, in our selected group of left-handed patients with left hemisphere injuries shows marked individual variations, as the following brief histories reveal. In only one case, however, was the speech loss so severe as to be permanently disabling.

Case 1 (No. 14718).—A private, aged 36, normally left-handed except for writing, sustained in May, 1944, a severe penetrating wound of the left hemisphere which caused gross destruction of the temporal lobe. No information is available as to his condition in the two years immediately following his injury, but when re-admitted in July, 1946, his general physical condition was good. Neurologically he showed a right upper quadrantic field defect, but remarkably little sensori-motor disability. Post-traumatic amnesia was assessed at between three and four weeks. An electroencephalogram showed unusually severe abnormality over a wide area in the left hemisphere. Psychological examination revealed a severe disability in the verbal field with marked impairment of reading and writing and severe dyscalculia. Spontaneous speech was sometimes nearly normal in grammatical form, choice of words, and enunciation, and at other times he managed to convey a good deal of what he wanted to say by drama, or by writing an odd word or figure. He had great difficulty in naming common objects, but expressive speech, reading, and writing were all more impaired than comprehension. He showed marked perseveration, and psychometric tests gave evidence of gross general intellectual loss.

When re-examined in September, 1947, his spontaneous speech showed an increase in vocabulary and he could name 95% of objects presented, but the so-called " telegraphic " style was still in evidence. Writing had improved but reading remained at the same rudimentary level. In addition, a slight receptive difficulty was suggested by his tendency to answer questions of his own instead of those put by the examiner.

In April, 1949, the patient's speech therapist reported that he was still suffering from a very severe expressive dysphasia, dysgraphia, and dyslexia. There was, however, a considerable improvement in his receptive powers, and he was continuing to make slow but steady progress in both expressive speech and reading. Before the war he had been a shipping clerk, but his disability prevented him from returning to his former occupation, and he was advised instead to take up some form of light manual work.

As regards handedness, the severity of dysphasia made it impossible to obtain a full and accurate account, but it was ascertained that before his injury he had used the right hand for writing and drawing (presumably owing to early training, though this was never established with certainty), but would throw and play tennis left-handed. He was left-footed.

A lesser but well-marked degree of speech impairment was shown by the following patient :—

Case 2 (No. 9616).—An officer, aged 23, naturally left-handed but partially ambidextrous, sustained a penetrating mortar shell wound of the left parieto-occipital region in August, 1944. Operation (Lieut. James) revealed that the dura was torn and the brain lacerated. Pulped brain, clot, and three bone chips were sucked out and a metallic foreign body removed. The bone defect, which was in the left mid-parietal area in the inter-auricular line, measured 5 × 3 cm. Neurologically his main symptom was a right-sided hemiparesis ; there was no hemianopia.

Initially he showed complete motor aphasia, but could understand the spoken word and obey simple commands. Three weeks after injury he was able to say " yes " and " no " and " good morning ", but the rest of his speech was slow and laboured and full of mistakes, which, however, he was quick to recognize. He was thus unable to name objects or read aloud but he could write down the names of objects correctly with his left hand and succeeded in writing a letter more or less correctly and without undue difficulty.

Five weeks later (about two months after injury) the word-mutilations had disappeared and he was speaking with what would pass for an ordinary stammer. Psychological examination at that time revealed little evidence of intellectual impairment apart from a slight residual dysphasia ; memory and abstract thought were almost unimpaired, but there was a tendency, probably dysphasic, to make slips, e.g., in letter writing. Pre-traumatic intelligence was judged to be well above average.

When re-admitted in December, 1945, his main physical disabilities were the remnants of his right hemiparesis and some sensory abnormalities in the right hand. Speech still showed a slight hesitation and slowness but on the whole had recovered very well. There was an occasional mild paraphasic error, and spelling was slow and a little uncertain. Reading and writing were both apparently normal, but there was some slight impairment in calculation. He had meanwhile been attempting a certain amount of difficult reading (e.g., Trevelyan's *English Social History*) and had found some difficulty in retaining the knowledge and ideas thus acquired. The more complex material he had to read some six or seven times before being able to memorize it, though comprehension of the meaning of individual sentences was little impaired. Once he had committed something to memory he considered that his powers of retention were as good as ever. He was also aware of a slight impairment of constructive thought, and when writing an essay was apt to lose the thread of the argument. In general, however, he had made a reasonably good recovery from his injury, and his

intellectual capacity had suffered only at the higher levels of conceptual thinking.

This improvement was subsequently maintained and he was able to manage successfully clerical work of a moderately responsible nature. When interviewed by one of us (M.E.H.) in November, 1950, he could add little to the account so far given. He stated that his memory was now "extraordinarily erratic", especially for names, yet on tests of immediate memory, both verbal and visual, he was easily within normal limits. His subjective feelings of memory impairment became more readily understandable in the light of his statement that at school his capacity for rote learning had been well above average. Certainly he had made an excellent recovery from his early dysphasia, the residual signs of which were obvious only under unfavourable conditions, such as fatigue or emotional stress. In view of his superior abilities it was perhaps too much to expect that he would ever regain full command of his intellectual powers, yet for all practical purposes he was back to normal.

Handedness was of considerable interest in this case. Though naturally left-handed, attempts had been made to convert him to right-handed writing over a period of about eight months, at the age of 8 or 9. These attempts he had resolutely resisted and he had in fact continued to write with his left hand, though acquiring a certain ambidexterity, especially for games, such as tennis, in which he would transfer the racket from his left to his right hand in order to avoid back-hand shots. In most things, however, he always preferred to use his left hand and regarded himself as primarily left-handed. He was also left-footed and left-eyed. He did not know of any left-handedness in his immediate family.

That dysphasia may involve a selective amnesia for words without any appreciable degree of general memory disturbance is commonly acknowledged. In the following case, however, where the residual dysphasic handicap was largely confined to a difficulty in word-finding, there was also evidence of a more widespread disorder in the memory sphere.

Case 3 (No. 2671).—A regular officer, aged 44, naturally left-handed, sustained a severe penetrating gunshot wound of the left fronto-temporal area in October, 1940. The bullet entered the left orbit and the point of exit was in the posterior part of the left temporal lobe. There was haematoma of the left orbit, and the left eye was destroyed. Operation (Mr. Summers and Mr. Oliver) was performed on the following day, revealing complete laceration of the orbital structures, and the remains of the left eye were removed. A second operation (Mr. Oliver) was performed a fortnight later, in which small pieces of necrotic bone were removed. The duration of post-traumatic amnesia was estimated as approximately six weeks, and retrograde amnesia as two days.

The patient was at first unconscious, and had a right-sided facial paralysis. Two days after injury he recognized his surroundings, and was able to ask for a bottle. Four days later he was reported as occasionally talking rationally, but it was not until three weeks after injury that he began to show any marked improvement in his mental condition. At this time he was described as "quite intelligent, but still aphasic". By the end of November, 1940, (seven to eight weeks after injury) the aphasia had practically cleared up, and his memory was said to be very good except for the names of people and places.

When examined in December, 1940, there was some loss of 2-point discrimination in the right hand but no other abnormal neurological signs, and he was reported to have made a good recovery from a very severe injury. Owing to post-traumatic amnesia he had no memory of the period during which he had been completely aphasic. His main complaint now was of his speech and memory. He had great difficulty in expressing himself and in recalling the names of objects; though usually able to produce the correct name eventually, he was occasionally at a loss, e.g., over a pencil-sharpener, where he was obliged to resort to pantomine. Except when tired he could grasp and define the meaning of words, but his reaction to questions was slow, suggesting that oral comprehension was probably a little impaired. Writing was affected to about the same degree as speech; thus he was at first unable to write a cheque to his satisfaction, could not think of the words he wanted, and when he did attempt to write the result was an illegible scrawl. He also had great difficulty in spelling even simple words. The following is a specimen of his writing at this stage: "I have a shoot of 2,500 acres, where game are very . . . . (long pause, and then) aborive (for "abundant"). No shooting has been done. I have been in Palestine, Iraq and Persia, the journey is best by travelling to Kurdistan. However it will be impossible to use your car when it is park then use your mule." Reading on the other hand was relatively easier: a little slow but, except when hurried, fairly accurate. He admitted to some difficulty in concentration and in comprehension of the total meaning, but was sure that he could identify and understand individual words. In addition to his specific loss of memory for words and for the names of acquaintances, there was evidence of a more general memory deficit, in that he was unable to recall recent events, even those after the period of post-traumatic amnesia, and would often forget things he wanted to do.

On his return to duty in May, 1941, (about seven months after injury) he was employed in an administrative capacity. Subjectively both speech and memory continued to improve, but he found himself frequently unable to memorize instructions. Thus he would visit his Commanding Officer, be told to do something, and by the time he had got outside the door he had forgotten what he had to do. This difficulty he overcame to some extent by writing down notes of all his orders. Physically he felt "as fit as hell"; his main complaint, in fact, was his memory, and in particular he was distressed by his inability to recall the names of racehorses.

When next examined in December of the same year,

he reported considerable further improvement in both speech and memory. His difficulties remained of much the same character, but he was learning to adjust to them and felt that he could manage his work more adequately. On the other hand a report from his Commanding Officer stated that "his memory cannot be relied upon, and his general behaviour is that of a man who has not entirely recovered from a serious injury". His difficulty in word-finding was still very marked in ordinary conversation, especially when he was searching for some precise expression, for example: "Battleships are no damn good, they're too big, they can't . . . . what's the bloody word I want, you can't hide them." Despite this difficulty, or possibly on account of it, he showed a remarkable capacity for making himself understood by circumlocution, gesture, and vocal inflection. His powers of oral comprehension remained appreciably retarded, and he still complained of difficulty in following a rapid conversation. Reading and writing were apparently back to normal, but spelling was still considerably disturbed, e.g., he mis-spelt about one out of every three words from the scholastic age level of 10 upwards (buisness, discease, promiscuse). His behaviour here suggested that he relied very much on the auditory word-image for his spelling. On psychological examination, his dysphasic handicap did not prevent him from obtaining a very superior score (38 plus) on the Stanford-Binet vocabulary test, and he was able to repeat seven digits forwards with an effort. His reproduction of the "cowboy story" was good. On a picture-naming test he scored 32 out of a possible 36 successes, his only obstacles being toy truck, dressing-table, comb, and alarum clock. Simple tests of visual memory revealed no significant impairment. A score of 33/60 on the Raven matrices hinted at some degree of general intellectual deterioration, although it was difficult to determine how much of the test result was due to his impaired efficiency and how much to his temperamental response to the test situation. The general impression was that "the impairment of learning and concentration is comparatively little and probably capable of further improvement; being an extroverted character and a versatile personality, he copes with his word-amnesia rather well and will do better still under conditions where his temperament does not carry him away".

Although he had had a generalized epileptic attack a few months previously, an electroencephalogram showed no evidence of abnormality, and there were no abnormal neurological signs.

Very little information is available as to his subsequent progress. When re-admitted briefly in August, 1949 (nearly nine years after injury), he stated that his general health was still good, and that he had been travelling all over the world. Subjectively his speech was almost normal, although he would occasionally bring out a word the exact opposite of what he had intended.

As regards handedness, this was another case of a naturally left-handed man who had been taught to write with his right hand at an early age. He did not lay any special claim to ambidexterity, and did not know of any left-handedness in his immediate family.

Two further cases of left hemisphere injury in which the dysphasic manifestations were less striking, may be reported more briefly.

Case 4 (No. 9531).—A private, aged 30, showed early global dysphasia with mild right-sided hemiparesis following a deep wound of the left frontal lobe penetrating to the ventricle; there was probably some degree of intellectual deterioration, but he achieved a good physical recovery and appreciable recovery of language functions within six months, although still liable to difficulties of word-finding 18 months after injury.

Case 5 (No. 10213).—A corporal, aged 32, who was naturally left-handed though partially ambidextrous, also presented a similar picture of early global dysphasia, with associated right hemiplegia, following a penetrating wound of the left parietal lobe. Gradual recovery from the hemiplegia took place over the first four months after injury, with similar improvement in language functions.

Cases of Right Hemisphere Injury

In the group of left-handed patients with right hemisphere injuries, variations in the severity of dysphasia were equally apparent, and in one case there was virtually no evidence of any disorder of this kind. Since we were concerned, among other things, to stress the liability of left-handed persons to speech disturbances even when the lesion is strictly confined to the left hemisphere, most of our available space has been given up to describing such cases. We shall, however, describe a case of right hemisphere injury in a left-hander sufficiently to indicate that a comparable language disability may be involved.

Case 6 (No. 9501).—A private, aged 21, strongly left-handed, was wounded by a shell fragment in the right mid-parietal region in August, 1944. The wound extended to the body of the lateral ventricle, and there was a large right extradural haematoma arising from the torn posterior branch of the middle meningeal artery. Operation (Lieut. Guthkelch) was performed within 24 hours for removal of a metallic foreign body and indriven bone fragments.

On examination the principal neurological signs were left spastic hemiplegia, supranuclear paralysis of the left side of the face and tongue, and some left-sided sensory loss. There was no hemianopia. Post-traumatic amnesia extended over about five days, retrograde amnesia being only momentary. There was almost complete motor aphasia with associated dysgraphia, but oral comprehension appeared fairly good despite some tendency to perseverate in his actions.

A fortnight later he still had great difficulty in producing a complete sentence, and was frequently at a loss

for the word he wanted. Objects were for the most part named correctly, though there were occasional failures. In addition he had considerable dyslexia, reading about 50% of words incorrectly, without any apparent insight into his errors.

A month after injury the dysphasia had improved to the extent that he now had no difficulty in sentence-construction, word-finding, or object-naming, but only in pronunciation. Reading, however, was still much impaired, and this defect was still in evidence three months later, when he tended to mispronounce some words and insert others which were not there, though without appreciably altering the meaning of sentences. Writing could not be tested properly owing to the hemiplegia. (The patient wrote with his left hand.) Calculation was not extensively tested, but he was distinctly slow at simple arithmetic, especially subtraction and multiplication. General memory was also affected, in addition to his specific disability in the verbal field.

On psychological examination four months after injury, he was only slightly dysphasic in ordinary conversation; reading was slow but fairly accurate. His spelling, which he claimed had been above average previously, was now very poor, and this in addition to the hemiplegia made letter-writing very troublesome. ("Raise" and "rough" correct; "pleasant" = "plesent"; unable to attempt "saucer", "answer" or "Wednesday".) In arithmetic he only just succeeded with two out of three average adult problems, and was very slow on these; here also he claimed to have been good before his injury. Verbal memory tests were not very well done: he repeated seven digits forward and five backwards, but took five attempts to master the Babcock sentence, and retained only 11 items out of 20 from a story of 20 lines. Regarding general intellectual capacity, vocabulary, general information, and comprehension (Wechsler) were all above average, but his score of only 39/60 on the Raven matrices suggested the possibility of some degree of intellectual deterioration at this stage. Moreover, although attention was said to be well sustained, there was a definite impairment of learning capacity on non-verbal tests. By the time of his discharge from hospital shortly afterwards he was expressing himself quite adequately, but complained that he still had difficulty with the longer words—"my tongue won't do what I want it to".

When re-admitted in August, 1945, a year after injury, he still showed moderate spasticity of the left leg and arm, with some sensory abnormalities. In the patient's own opinion language functions, memory, and general intellectual capacity seemed to have improved almost up to his pre-traumatic level, although he admitted to some difficulty in concentration, e.g., when playing chess or writing letters. On examination, however, his speech was still slightly hesitant and calculation slow.

A second operation (Capt. Northcroft) was carried out to remove an indriven bone fragment. Degenerated cortex was found adhering to the dura.

When re-examined four months later he was able to read with normal fluency provided he took his time, and he had learnt to write quite well with his right hand, though he was still apt to make mistakes. On enquiry, he admitted that spontaneous speech still caused him a little difficulty, but it appeared almost normal except under stress. On an object-naming test he hesitated on only one out of 12 objects (wrist-watch = "winder").

Owing to the development of post-traumatic epilepsy he was detained in hospital under observation for the greater part of the next 18 months. When finally discharged in May, 1947, he was able to resume his pre-war work (hosiery dyeing) for a short time.

Regarding handedness, there can be no question that this patient was strongly left-handed before his injury, and had always written with his left hand. Since his injury he has been able to do very little with his left hand owing to residual hemiplegia.

Case 7 (No. 8846).—On an officer, aged 32, who had been left-handed apart from writing, both the injury and the ensuing dysphasia were broadly comparable to the preceding case. Since, however, this case presented in addition to the dysphasia certain other features, notably impaired visualization and topographical loss, which were thought to have a special bearing on the problem of minor hemisphere function, it has been made the subject of a separate communication (Humphrey and Zangwill, 1952).

In our next case the outstanding feature was a permanent agraphia, other language functions being only temporarily impaired.

Case 8 (No. 9982).—A corporal, aged 26, naturally left-handed though partially ambidextrous, was wounded by a shell fragment in the right frontal lobe in September, 1944, causing extensive destruction of brain tissue in the fronto-parietal region. Operation (Capt. Turner) was performed to remove a large, indriven bone fragment, and necrotic brain was sucked out, leaving a shallow laceration under a large dural defect. Early neurological signs included a left hemiplegia with facial paresis, sensory and Babinski loss, and left homonymous hemianopia.

When first examined he was sufficiently conscious to obey simple commands, but would not attempt to speak or answer questions. Three weeks later it was still difficult to elicit other than monosyllabic answers from him: moreover his speech was slurred, though some of his words were quite clearly enunciated. He had no apparent difficulty in naming objects. When asked to write his name he seemed quite unable to put pencil to paper, merely remarking "it might be signing my own death warrant". In attempting to read aloud he would read several words at a burst, then miss out a number and pick up a few more later in the paragraph. He showed no sign of understanding simple written commands. A month after injury his speech functions had recovered very well, apart from writing: thus he was able to carry out complicated oral commands, could express himself well, read normally and give the

gist of what he had just read, yet he could manage no more than an indecipherable scrawl with his right hand, though he seemed quite confident that he would be able to write his name. (It must be borne in mind, however, that the patient had always written with his left hand for preference before his injury, though he claimed to have been able to write with his right hand to a limited degree.) He also showed considerable impairment of calculation: simple feats of subtraction or multiplication were within his grasp but he failed consistently in his attempts to add double figures. He further complained of difficulty in recognizing people and in finding his bed in the ward.

Psychometric tests in December, 1944, gave evidence of marked intellectual deterioration: vocabulary, general information, and comprehension (Wechsler) were somewhat above average, corresponding to IQ 110, but he scored under 20 on the progressive matrices, and memory and learning capacity were noticeably impaired. Spelling was about average. At the time of his discharge from hospital in May, 1945, his general condition was almost back to normal, but his ability to write with his right hand had not improved.

In May, 1946, he was re-admitted following persistent attacks of traumatic epilepsy. Meanwhile the left leg had improved immensely, but there was still severe spasticity of the left arm. There was partial improvement in the hemianopia. He stated that his powers of reading had improved tremendously, and he was now able to read a book right through. Writing, on the other hand, was very little improved. Thus an examining neurologist commented: "A very interesting case of a deep fronto-parietal injury in a left-handed man. Complete recovery of speech except for almost complete agraphia, suggesting that the 'writing centre' is in this case entirely right-sided but that the rest of his speech functions were bilaterally represented". There was no evidence on psychometric tests of any appreciable improvement in his general intellectual level. Calculation was still definitely impaired, and there was probably some verbal memory loss; for example, he was unable completely to master the Babcock sentence in the course of 10 trials. His behaviour in the test situation was described as very "concrete" in Goldstein's sense.

More recent information indicates that the hemiplegia and intellectual loss have left him permanently disabled, as might have been expected from the severity of his injury.

The patient was naturally left-handed, but some attempt had evidently been made to teach him to write with his right hand since he claimed that he had previously been able to write with either hand, though normally preferring his left for this and most other purposes.

The two remaining cases of right hemisphere injury deserve brief mention.

Case 9 (No. 9054).—A private, aged 31, who was wounded by a shell fragment high up in the posterior frontal region, never gave any definite clinical evidence of true dysphasia, but about six months after injury an examining psychologist found, on the evidence of selected verbal tests, a slight residual impairment of language in both its expressive and receptive aspects. Spelling was also affected. He made a good general recovery, yet even as long as two years after injury, when he was admitted for skull repair, an examining neurologist commented, "I think there is a minimal nominal dysphasia and slight dysarthria". The patient also complained of frequent memory lapses. Before his injury he had been left-handed for most purposes other than writing, but subsequently he found great difficulty in adapting to the change-over that was forced upon him by the sensory loss in his left hand.

Case 10 (No. 10880).—A lance-corporal, aged 31, naturally left-handed but a right-handed writer, sustained a severe injury of the right mid-parietal region, causing left hemiplegia, cortical sensory loss, and slight slurring of motor speech but no true dysphasia. (Indeed, he remembered being able to speak immediately after injury.) There was no appreciable intellectual loss.

(A similar case of severe right hemisphere injury producing no obvious language disability in a patient who was entirely left-handed has since come to our notice.)

Analysis of Case Material

Site of Injury.—The anatomical distribution of left and right hemisphere injuries in terms of areas of the cerebral cortex is shown in Table I.

TABLE I
SITE OF WOUNDING IN THE CASES STUDIED

Site of Wound	Left Hemisphere	Right Hemisphere
Parietal	1	2
Posterior parietal ..	1	1
Fronto-parietal	1	2
Temporal	1	–
Fronto-temporal	1	–

Handedness.—All patients had regarded themselves as predominantly left-handed before their injury. Three patients in either group had been taught to write with the right hand, while the other two had written with the left hand up to the time of injury. Further, at least two cases of left hemisphere injury and at least one (possibly two) of right hemisphere injury had shown ambidextrous tendencies. One may suggest that the latter were certainly present to a limited degree in all cases of left hemisphere injury, but more doubtfully so in the right hemisphere group. Residual physical disabilities resulting from the injury compelled an almost complete change of handedness in all the right hemisphere cases, although only two patients (Cases 6 and 8) had to change their writing hand. A peculiar difficulty in adapting himself to the change of handedness was reported by only one

patient (Case 9), although no doubt this was experienced to some extent in all cases; one previously left-handed writer (Case 6) learnt successfully to write with his right hand in the year following his injury.

Language Disorders.—The distribution of language disorders in the two groups (left and right hemisphere injuries) is given in Table II.

TABLE II

DISTRIBUTION OF LANGUAGE DISORDERS IN THE CASES STUDIED

	Left Hemisphere Injuries					Right Hemisphere Injuries				
Case No.	1	2	3	4	5	6	7	8	9	10
Expression and/or word-finding ..	+	+	+	+	+	+	+	+	+	−
Comprehension	+	−	+	+	+	−	+	+	?	−
Reading ..	+	+	(+)	+	+	+	+	+	−	−
Writing ..	+	(+)	+	?	+	?	+	+	−	−
Spelling ..	+	+	+	+	?	+	−	−	+	−
Calculation ..	+	−	?	−	−	+	+	+	+	−
Spatial sense..	−	−	−	−	−	−	+	+	−	−

Plus sign = impaired; minus sign = no evidence of impairment; (+) = probable slight impairment.

Owing to the varying intervals between successive examinations, the fact that the cases were seen by different examiners at different stages, the difficulties which, in any case, would be involved in trying to determine at all accurately the degree of impairment, and in deciding whether such impairment is to be regarded as permanent, no attempt has been made to differentiate in Table II between mild and severe, or transitory and permanent, grades of defect. Broadly speaking, however, it may be noted that in the left hemisphere group recovery of language functions after periods varying from six months to two years was practically complete in Case 2, very satisfactory in Cases 3 to 5, and extremely limited in Case 1 (a very severe injury, involving gross loss of brain substance). Speech therapy was given in Cases 1, 2, and 4. In the right hemisphere group, language recovery was complete in Case 7 with the help of speech therapy, and very satisfactory in Case 6; in Case 8 writing was the only language function permanently impaired; in Case 9 the degree of original impairment was relatively slight, while in Case 10 language was never affected apart from a mild slurring of motor speech. On the other hand calculation was permanently impaired in all the right hemisphere injuries except Case 10. Disturbances of spatial sense were confined to two cases in this group. Residual dysphasia in almost all cases of both groups took the form of a slight hesitancy of speech and difficulty in word-finding.

The relative incidence of the various defects is illustrated numerically in Table III.

TABLE III

RELATIVE INCIDENCE OF DEFECTS IN CASES STUDIED

Defect	Side of Lesion	
	Left	Right
Global dysphasia	4	2
Expressive and/or nominal dysphasia ..	5	4
Receptive dysphasia	4	2
Dyslexia	5	3
Dysgraphia	4	2
Spelling defects	4	2
Dyscalculia	1	4

Thus if we exclude dyscalculia, which apart from the one case of severe and permanent dysphasia, where the lesion was left-sided, was confined to the right-sided cases, the incidence of dysphasic and other symptoms is consistently higher in the left hemisphere group.

General Intellectual Capacity.—There is good evidence that Cases 2 and 3 of the left hemisphere, and Case 7 of the right hemisphere, injuries were men of superior intelligence, as judged by personal history and performance on the Wechsler tests of vocabulary, general information, and comprehension. The remainder were probably all of at least average intelligence and in some cases a little above average. The balance between the two groups is approximately even in this respect. Varying degrees of general intellectual deterioration, as measured by tests of sorting and of reasoning by analogy, were demonstrated in three cases of left hemisphere injury (Nos. 1, 3, and 4) and in all the right hemisphere injuries with the exception of Case 10. This deterioration was severe and caused permanent incapacity in Cases 1 and 8 (both very extensive lesions, left- and right-sided respectively), milder and with less harmful consequences in the remaining cases. A specific memory defect, as distinct from severe loss of general intellectual capacity, was conspicuous in Cases 3 and 9, left- and right-sided injuries respectively.

Physical Signs.—Hemiplegia was severe and residual in Cases 2 and 5 of the left hemisphere injuries, and in all the right hemisphere injuries except Case 9, where it was mild and transitory. A lesser degree of early hemiplegia was also shown by Cases 1 and 4, but there was none in Case 3 (left hemisphere injuries). Varying degrees of cortical sensory loss were demonstrated in all cases

of right hemisphere injury, but only in Case 2 of the left hemisphere injuries. Hemianopia was present in Cases 1, 7, and 8. Apart from the above disabilities, a good physical recovery was achieved in all cases.

Discussion

The fact which emerges most clearly from this study of the effects of unilateral brain lesions in left-handed patients is that some evidence of " language disorder ", this broad term being intended to cover disturbances of reading, writing, spelling, calculation, and verbal memory or learning, in addition to dysphasia in the narrower sense, was found in one form or another in all cases except one, irrespective of the laterality of the lesion. It is true that one of the criteria determining the selection of our cases was that " the lesion must be such as would be expected to interfere with speech functions if the affected hemisphere were the dominant one " ; yet if left-handedness were correlated with " right-brainedness " to the same degree as right-handedness with " left-brainedness, " as has commonly been assumed, then dysphasia would have been expected to occur only in the right hemisphere injuries. Our findings go even further against the traditional view in that the various forms of language disorder, with the exception of dyscalculia, show a higher incidence in the cases of left hemisphere injury.

In drawing attention to this apparent anomaly we cannot claim to have made an entirely new discovery. In the nine cases reported by Chesher (1936) of persons with mixed handedness, the lesions giving rise to dysphasia were again almost equally divided between the left and right hemispheres, while the same lack of uniformity regarding cerebral dominance has been observed by Conrad (1949) and by Penfield and Rasmussen (1950) even in persons who were not noted for any mixture of handedness. It would appear, however, that the mere fact of writing with the right hand, in a person who is strongly left-handed for most other purposes, is regarded by some writers as an example of mixed handedness. In some of the cases studied by the other authors quoted here handedness may have been " mixed " in this sense. Moreover, the same slight, and not necessarily significant, preponderance of left hemisphere lesions was observed by Conrad in his series of left-handed aphasics. Yet no detailed account of dysphasic manifestations in their cases is offered by any of the above-mentioned authors, and so far as we are aware none of the more elaborate studies of aphasia so far published have been brought into relation with problems of handedness. On such grounds alone it is hoped that our own detailed presentation will prove justified.

The fact that only one of our carefully selected cases was free from dysphasic symptoms lends further support to the hypothesis put forward by previous writers that cerebral dominance either does not occur at all in the so-called left-handed, or if it does occur, tends to be less well developed than in the general run of right-handed persons. It is true that no detailed study of right-handed aphasics has been included here ; yet in support of our contention the following facts may be adduced. Of 492 cases of penetrating brain injuries studied from the point of view of handedness, site of lesion and presence or absence of dysphasia, 436 were known to be right-handed ; of these 105 were still dysphasic at the time of their discharge from hospital, yet the lesion was with one single exception confined to the left hemisphere. Thus it would be impossible to select from this group of right-handed aphasics 10 cases showing a comparable division between left- and right-sided lesions, while it is extremely unlikely that, if 10 cases were selected at random from the total right-handed group of 436 cases, only one would be free from dysphasia.

In regard to individual differences of handedness in our 10 cases, the available information was too limited for us to apply the method of assessment and classification put forward by one of us elsewhere (Humphrey, 1951). Broadly speaking, however, our patients were all primarily left-handed, though some were partially ambidextrous. It is thus remarkable that only two cases, left-handed and right-handed writers respectively, showed an appreciable degree of " right-brainedness " so far as spoken language was concerned ; in one other case there was good evidence of left-handed writing being predominantly governed by the right hemisphere, according to expectation, yet the remaining seven cases showed a marked tendency toward " left-brainedness " in all their speech functions.

The fact that only three of our patients were under 30 at the time of injury, all being left-handed writers, is of considerable importance in the present context. Of the rest only one had remained a left-handed writer, the others having been compulsorily shifted at an early age ; in two of the left-handed writers also there was some history of early interference with writing habits. If we take into account the conclusion reached by Humphrey (1951) that the early conversion of a naturally left-handed individual to right-handed writing is liable to influence his later manual habits not only in regard to writing itself, but also secondarily in

promoting a greater tendency toward ambidexterity and a more frequent preference for the right hand in situations favouring its use, then it seems reasonable to assume that a corresponding influence is likely to be exerted on such an individual's ultimate cerebral organization. If this is the case, then we should also draw attention to the fact that most of the patients included in the present study were born at a time when social pressure against left-handedness in general, and left-handed writing in particular, was still fairly strong. Now that the pendulum has swung the other way, and children are in many cases even actively encouraged to write with the left hand if so inclined, it is theoretically possible that "right-brainedness" will gradually gain in both strength and frequency among the naturally left-handed.

One final point merits brief discussion. It has already been suggested that cerebral dominance may be relatively undeveloped in many left-handed persons. This would in turn imply that cerebral representation of the language functions in such cases is bilateral, at any rate to a greater degree than in most right-handed people (Chesher, 1936). From this it would follow that handedness was a possible or even an important factor in speed of recovery from dysphasia, since the other, uninjured hemisphere would in these circumstances be far more ready to take over full control of the speech functions when called upon to do so. Unfortunately our material does not throw any further light on this question. It is true that our left-handed patients achieved an excellent recovery of language, except in those two cases where the injury was exceptionally severe; yet this has no final significance without a control group of right-handed aphasics with broadly comparable lesions. While it would be easy enough to assemble such a group of cases, the assessment of comparative rates of recovery through the study of case histories would be a far more problematic undertaking. Careful study and psychological assessment of aphasic patients personally and over a long period, coupled with a full investigation of their handedness and other aspects of laterality (Humphrey, 1951), will be necessary if this tentative conclusion is to be tested as systematically as it deserves; while at the same time we must realize that the problem of recovery from aphasia cannot be approached from the neurophysiological viewpoint alone, since various other factors, including above all the personality of the patient, are undoubtedly involved. By drawing attention to this apparent peculiarity in the cerebral organization that is associated with left-handedness we may hope to stimulate further research along these lines, while at the same time stressing the importance of obtaining accurate information as to handedness in the course of routine neurological examination of patients with brain injury.

Summary

Ten carefully selected cases of unilateral brain lesion (five left-sided and five right-sided) in naturally left-handed patients of good intelligence were studied with reference to the cerebral representation of language functions.

Dysphasia was present in all cases of left hemisphere lesion and in all but one of the right hemisphere cases. On balance the dysphasic symptoms were more severe in the former group, although defects of calculation were more prominent in the latter.

Some theoretical implications in regard to handedness and cerebral dominance are discussed.

We wish to thank Dr. W. Ritchie Russell for his generous encouragement and kind permission to quote extracts from the case records of the Head Injury Advice Bureau, and to interview patients under his care.

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CEREBRAL DOMINANCE IN CASES OF READING DISABILITY

BY

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In an extensive review of the literature on reading disability Hallgren (1950) finds a consensus of opinion among most authors that the incidence of severe cases of dyslexia among otherwise normal school-children is about 1% ; and this agrees well with the most recent finding in this country, reported in the Ministry of Education (1950) pamphlet " Reading Ability ", that 1·4% of children leaving school were illiterate. Hinshelwood (1917) described individual cases of this disability under the designation " congenital word blindness ", but it was Orton (1937) who attracted attention to the disturbances of lateral dominance in the patients he studied. (I am inclined to subscribe to Orton's and Hallgren's criticism of this term, and to agree with the latter that the diagnosis " specific dyslexia " is suitably obscure, adequately descriptive, and carries no theoretical implications.)

Orton observed that hand or eye preferences were often not consistently unilateral ; and set up the hypothesis that

> " the existence of demonstrable mixtures between right and left motor preferences . . . implies that comparable intergrading may exist between the critical areas for the various fractions of the language faculty in the two hemispheres of the brain, thus giving rise to a series of developmental disorders in language " (1937).

These disorders arise because

> " learning to read . . . entails the elision of one of the two antitropic records or engrams (in opposite hemispheres), and faulty or incomplete elision would result in uncertainty in mnemonic recall of orientation and progression " (1943).

Subsequently, a number of investigations has been reported of the lateral preferences of dyslexic children, the evidence in some cases supporting, and in others opposing, Orton's interpretation. Although not confirmed by Hallgren's investigation, perhaps the most consistent observation has been that a high proportion of these patients show a left-eye preference (Macmeeken, 1939) or cross dominance, right-handed but left-eyed (Harris, 1947). Some authors (e.g. Wile, 1942 ; Blau, 1946) contend that right-eye dominance is more conducive to the left-to-right direction of gaze necessary in reading ; while Orton (1943) considered " that left-eyedness is not the cause of the reading disability but rather indicates that there is present in these persons a tendency toward use of the right hemisphere of the brain—i.e. leftsidedness ". Selzer (1933), on the other hand, found that, of a group of normal children, the left-eyed tended to be faster readers.

It is difficult, however, in view of the bilateral projection of each retina upon the cerebral hemispheres, to see how the demonstration of ocular preference can indicate the dominance of either hemisphere. It is more relevant in this connexion to study the " preference " for one or other of the homonymous half-fields ; but here again different methods of investigation have produced conflicting results. Stevens and Ducasse (1912) found that their (right-handed) subjects tended to overestimate extents in the right half-field of vision ; White and Dallenbach (1932) that for right-handed subjects the left half-field had greater " attention value " and the right for left-handers ; and LaGrone and Holland (1943) found an association between right-handedness, right-eyedness, preference for the left half-field, and higher reading ability.

The present study concerns the use of the Phi Test of lateral dominance in visual function, described by Jasper and Raney (1937), in which a comparison is made of the extent to which the phenomenon of apparent movement (" phi ") is seen in the two half-fields of vision. Examining a group of normal school-children with this procedure, Jasper and Raney found a close agreement between the hemispheral dominance indicated by the test and by subjects' handedness, and the present investigation was undertaken in the expectation that results might support, or otherwise, Orton's view that specific dyslexia " has its neurological basis in confusion in cerebral dominance " (1942). Jasper had earlier (1932) found that seven out of 19 stutterers saw no apparent movement on this test, and concluded that

> " unilaterality in general neural organisation is expressed in the field of perception as well as in the

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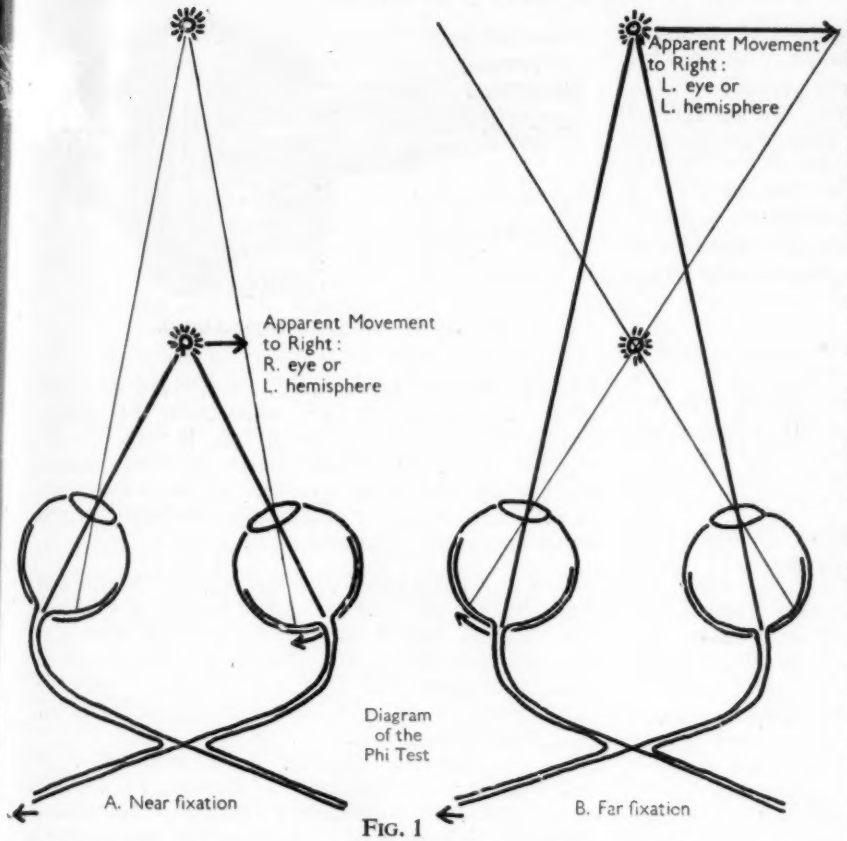

FIG. 1

field of manual preference. The . . . test . . . clearly demonstrated the lack of unilaterality on the part of stutterers as compared with right- and left-handed normal speakers."

Testing Procedures

The Phi Test.—The essential feature of this test consists of the exposure of a small point of light, which the subject fixates, which is extinguished and followed after an interval of 80 to 100 m.secs. by the appearance of two points of light, one on either side of the line of fixation ; these are extinguished and the central point again illuminated ; and the cycle is repeated until the subject reports apparent movement of the central light toward one of the side-lights. A consideration of the neuro-anatomical relations of the retinae makes it clear that the perception of apparent movement from the fixation point to one of the side lights must involve the visual pathway of the opposite hemisphere. An additional advantage of Jasper and Raney's procedure is that, as there are in fact only two points of light, alternately illuminated, and the " side-lights " are actually the double images formed by the non-fixated light, there are two possibilities for fixation ; and, by comparing the subject's report when the far light and the near light are being fixated, it is possible to deduce whether the apparent movement is a function of eye-dominance or of " hemisphere-dominance ". Fig. 1 shows the relationships involved in the two positions of fixation.

The apparatus consisted simply of a long, light-tight box, in which the near point of light was 10 in. from the viewing-slot and the far one 60 in. The lights were alternately illuminated, as in Jasper and Raney's apparatus, by a commutator driven by a variable speed gramophone motor. The subject was required to fixate the near light, and then to look at the alternation between this and the side-lights, until he reported consistent apparent movement lasting two minutes, or for 10 minutes, whichever was the shorter time. The time intervals of illumination were then changed and the experiment repeated with the far light as fixation point In each case, the direction of movement, if reported, was checked by requiring the subject to indicate it on a diagram of the three points of light

Handedness.—As Blau (1946) and Burt (1950) have pointed out, hand preference is more consistent, and for the majority of subjects more frequently right-sided, the greater the skill involved in the operation. Since the present study is concerned specifically with language functions, it was thought that hand preference in relation to these functions would be the most relevant criterion : this was determined simply by requiring the subject to write simultaneously with both hands the numbers from 1 to 10 while keeping his eyes closed (Harris, 1947), and noting the hand showing the better coordination.

Eye-preference.—Buxton and Crosland (1937) have demonstrated the reliability of simple tests of ocular preference. In the present study it was determined by requiring the subject to look, through a hole in a card held in both hands about a foot from his nose, at an object to his left, to his right, and to his left. If there was any variation in the eye used, three more observations (right, left, right)

were made, and the eye most frequently used was noted. To determine the possible relevance of " direction of gaze " some subjects were also shown a reproduction of Jastrow's (Fig. 2) ambiguous figure (Blau, p. 134) and asked what it looked like to them.

Intelligence.—Intelligence was tested on eight of the 11 items of the Wechsler-Bellevue adult scale,* and visual retention with the Stanford-Binet Form L " memory for designs " item.

Reading Ability.—This was tested quantitatively on Burt's (1947) Scholastic Test 1 and qualitatively on Schonell's (1948) Diagnostic Tests R6 and R7. Writing (spelling) was tested on Burt's Scholastic Test 6.

Case Histories

Case 1 (N.H.2003).—A packer, aged 17, was first seen four years ago, on account of reading disability. He is one of eight children, two of whom are left-handed, but no other abnormality was noted. No neurological abnormality was detected, and the psychiatrist and social worker found no abnormality in the patient or his background.

He was quiet and hesitant in speech, but quick on performance tests. Bellevue equivalent scores were: digit span, 6; arithmetic, 7; similarities, 11; vocabulary, 8; picture arrangement, 14; picture completion, 14; block designs, 12. He managed to read the first half of Schonell's R2, with considerable assistance, very poorly, but answered all the questions correctly. On the Phi Test he saw no apparent movement on near fixation, and only occasionally reported some movement, left or right, on far fixation.

Case 2 (N.H.8877).—A schoolboy, aged 13 years and 7 months, was first seen three years ago, on account of reading disability. No physical abnormality was noted. His elder brother had no reading disability. At that time the patient " reversed " almost every word he tried to read.

He was neat, emphatic, and self-assured. Bellevue scores were: digit span, 7; arithmetic, 7; similarities, 8; vocabulary, 7; picture arrangement, 8; picture completion, 12; block designs, 7; digit symbol, 4. He read and answered Schonell's R2 at the 8-year level, and made reversals only on R7. Apparent movement was intermittent, in either direction, on both fixations.

Case 3.—A builder's labourer, aged 28, was first seen three years ago on account of reading disability, from which he had suffered since his schooldays. Following a closed head injury he had been under treatment for anxiety symptoms, but had no physical abnormality.

He had a new house and opportunity for gardening, and his psychiatric state had improved considerably. His wife had been trying to help him with reading and writing. Bellevue scores were: digit span, 4; arithmetic, 7; similarities, 7; vocabulary, 7; picture arrangement, 6; picture completion, 10; blocks, 10; digit symbol, 8. He could not even read letters accurately, though he made no reversals. Apparent movement was seen consistently on near fixation, and intermittently on far fixation, always to the right.

FIG. 2.—Jastrow's ambiguous figure.

Case 4 (N.H.14903).—A schoolboy, aged 10 years and 3 months, was admitted to hospital because of a history of a fall, with a small occipital laceration but no loss of consciousness, five years previously. There was no physical abnormality; the E.E.G. was " probably within normal limits for this age, although perhaps rather less organized than is usual ".

He was alert and cheerful. Bellevue scores were: digit span, 3; arithmetic, 1; similarities, 7; vocabulary, 5; picture completion, 8; blocks, 4. He made a number of reversals in reading and writing, but managed to read the first half of Schonell's R2 and answered all the questions correctly. Apparent movement was reported intermittently, in either direction, on near fixation, and predominantly to the right on far fixation.

Case 5 (N.H.12809).—A schoolboy, aged 13 years and 9 months, was admitted to hospital on account of his backwardness and mildly delinquent behaviour. There was no physical abnormality; air-encephalography showed no evidence of cerebral atrophy or hydrocephalus; an E.E.G. had had some unusual features, but on the whole was " acceptable at this age ".

He was quiet and rather apprehensive, but cooperated well on testing. Bellevue scores were: digit span, 6; arithmetic, 6; similarities, 5; vocabulary, 6; picture arrangement, 9; picture completion, 11; blocks, 11; digit symbol, 4. He read the first half of Schonell's R2 with nine errors very slowly, but answered all the questions correctly, and made reversals only on R7. Very little apparent movement was reported, either way.

Case 6 (N.H.18230).—A transport depot worker, aged 15 years and 5 months, was first seen two years ago, on account of his retardation. There was no physical abnormality, and although there had been inter-parental trouble at home, all the other six children (one left-handed) could read and write.

He had a stammer, but was alert and cheerful. Bellevue scores were: digit span, 7; arithmetic, 7;

* Information, comprehension, and object assembly were omitted.

similarities, 8; vocabulary, 7; picture arrangement, 11; picture completion, 14; blocks, 10; digit symbol, 7. He read and answered Schonell's R2 at the 9-year level, and made a reversal only on R7. Apparent movement was not reported on near fixation, but was seen simultaneously in both directions on far fixation.

Case 7 (N.H.22351).—A schoolboy, aged 10 years and 4 months, attended the hospital on account of epilepsy. There were no abnormal physical signs, but his scholastic retardation was noted. The E.E.G. was complex but consistent with idiopathic epilepsy.

He was quiet and economical of words, but at the same time appeared at ease and cooperated on the tests. On the Terman-Merrill scale his mental age was 8 years and 3 months, with early failures on verbal items; on Kohs' block test it was 12 years and 11 months. He made no reversals. Apparent movement was occasionally seen, either way, on near fixation; and predominantly to the right on far fixation.

Case 8 (N.H.24615).—A schoolboy, aged 11 years and 2 months, attended on account of reading disability. No physical or psychiatric abnormality was found.

He was cheerful and cooperative. Bellevue scores were: digit span, 6; arithmetic, 9; similarities, 11; vocabulary, 8; picture arrangement, 10; picture completion, 10; blocks, 10; digit symbol, 6. He made reversals in reading but not in writing. He reported hardly any apparent movement, either way, on both fixations.

Case 9 (N.H.30319).—An engine-fitter, aged 31, attended on account of headaches following a slight head injury at football, but giving a history of reading disability since his school-days. There was no physical abnormality and a radiograph and E.E.G. were normal.

On testing, there was no evidence of dysphasia or organic deterioration. Bellevue scores were: digit span, 6; arithmetic, 6; similarities, 6; vocabulary, 8; picture arrangement, 7; picture completion, 14; blocks, 9; digit symbol, 7. He made one reversal in writing, and three on Schonell's R7. He reported no apparent movement on either fixation.

Case 10 (N.H.31000).—A man, aged 20, at the age of 16 had been certified under the Mental Deficiency Acts, and since then had been detained in an institution. No physical or psychiatric abnormality was found: the E.E.G. was reported as being "borderline" at his age.

He was, perhaps understandably, rather anxious at the beginning of the tests, but became more confident as he found he could do them. Bellevue scores gave: digit span, 7; arithmetic, 7; similarities, 8; vocabulary, 6; picture arrangement, 12; picture completion, 14; blocks, 15; digit symbol, 8. He made no reversals in reading or writing. He reported no apparent movement on either fixation.

Case 11 (N.H.32010).—An upholsterer, aged 34, attended on account of his reading disability. There was no physical or psychiatric abnormality.

He was short, slightly built, and appeared to be a little nervous about the examination, but became more confident on performance tests. Bellevue scores were: digit span, 6; arithmetic, 3; similarities, 10; vocabulary, 9; picture arrangement, 7; picture completion, 9; blocks, 11; digit symbol, 7. He made some reversals on Schonell's R7. Apparent movement was reported very occasionally, largely to the right, on both fixations, and was once reported as "both ways".

Case 12 (N.H.33864).—A schoolboy, aged 11 years and 3 months, was admitted to the hospital for investigation of a possible relation between a chronic left otitis and mastoiditis and his scholastic retardation. There was, however, no physical evidence of this: a radiograph of the skull did not indicate spread of infection. An E.E.G. was asymmetrical but "within normal limits for the age"; and audiometry showed normal hearing in the right ear.

He was a quiet, shy little boy, but applied himself enthusiastically to the tests. Bellevue scores were: digit span, 7; arithmetic, 7; similarities, 8; vocabulary, 6; picture arrangement, 10; picture completion, 10; blocks, 12; digit symbol, 5. He read and answered Burt's Test 5 at the 9-year level, but made no reversals. He reported no apparent movement on either fixation.

Results

The responses of normal subjects on the Phi Test have been described in some detail by Jasper, who examined 77 adults, and by Jasper and Raney, with 43 school-children. In the present study, 12 normal subjects (i.e. with no reading disability) of ages ranging from 9 to 25 years, but not otherwise equated with the patients, were tested, and their responses were similar to those of the subjects tested by Jasper and Raney. All except one reported consistent or predominantly one-sided apparent movement within eight minutes of beginning each phase of the test, and two of the subjects, besides reporting unilateral apparent movement, also reported occasions on which the central light appeared to "split", and jumped to both sides simultaneously. Four of the subjects were shown Jastrow's figure, and all reported that it looked like a bird or a duck.

The results of the 12 patients with reading disability are summarized in Tables I and II. It will be seen from Table I that only three of the patients perceived enough consistent apparent movement to suggest the dominance of one hemisphere, and of these only one (Case 3) reported the phenomenon with anything like normal definition. Two patients (Cases 6 and 11) reported the occasional appearance of the central light "splitting". At the same time, while the majority (nine) of the patients showed some tendency to "reversal" either of letters or of Jastrow's figure, this did not appear to bear any consistent relationship to handedness, eyedness, cross-dominance, or to the type of response on the Phi Test.

TABLE I

RESULTS IN PATIENTS WITH READING DISABILITY

Case	Preference		Reversals*	Jastrow's Figure	Apparent Movement	
	Hand	Eye			Direction	Dominance
1	R	R	0	Bird	Very little, right and left	Indefinite
2	L	L	+	Rabbit	Very little, right and left	Indefinite
3	R	R>L	0	Rabbit	Predominantly right	L. hemisphere
4	R	L	++	—	Intermittent near : but right far	L. hemisphere or L.eye
5	R	R	+	Duck	Very little, right and left	Indefinite
6	L	R	+	Duck	None near : both far	None
7	R	L	0	—	Right on far fixation	L. hemisphere or L.eye
8	R	R	++	Rabbit	Very little, right and left	Indefinite
9	R	R	+	—	None	None
10	R	L	0	—	None	None
11	L	R	+	—	A little, right	L. hemisphere
12	R	R	0	Rabbit	None	None

*+ signifies reversals shown only on Schonell's R7 : ++ signifies reversals shown more frequently.

TABLE II

RESULTS IN PATIENTS WITH READING DISABILITY

Case	Chronological Age	Mental Age (Non-verbal)	Reading Age	Writing Age	Reversals*	Memory for Designs†
1	17	>15·6	8	7	0	—
2	14	11·9	9	7	+	++
3	28	12·7	<5	0	0	++
4	10	10·3	6	6	++	+
5	14	12·9	7	7	+	++
6	15	>15·6	8	7	+	++
7	10	12·11	6	6	0	0
8	11	13·0	7	6	++	++
9	31	13·6	10	7	+	++
10	20	>15·6	12	7	0	++
11	34	12·7	6	6	+	0
12	11	13·6	10	8	0	++

*+ and ++ are as in Table I.
†+ signifies a pass at the 9-year level ; ++ signifies a pass at the 11-year level.

Table II indicates the discrepancies between the patients' mental ages (on the performance half of the Bellevue scale) and their reading and writing achievements. It will be seen that the extent of these does not appear to be related to the incidence of reversals. The table also records the good performance of the majority of the patients on the visual retention test.

Discussion

The cases reported conform to the usual description of the syndrome of specific dyslexia* ; their visual perception was normal (cf. Eames, 1948), as was retention of visual material (cf. Fildes, 1921), but they showed a reading retardation of three or more years in comparison with their mental age as measured on non-verbal tasks, and a number of them showed a tendency to reversal of letters, syllables, or of an ambiguous figure. An additional defect, which has been studied in considerable detail by Fildes and noted also by Orton and by Wolfe (1941), is the difficulty shown by these patients in " repicturing or rebuilding in the order of presentation *sequences* of letters, of sounds, or of units of movement " (my italics) ; a difficulty in acquiring *series* (Orton, 1937). The present group of patients showed this in their relatively poor digit span scores.

The coincidence of a tendency to reversal and of a difficulty in acquiring series may not, on the face of it, seem an unexpected finding, but its theoretical significance lies in the fact that, in Orton's view, it is the tendency to reversal which disturbs the acquisition of series, and arises, according to him, from a failure to elide the mirror-image engrams in the non-dominant hemisphere. The significance of this tendency to reversal has, however, been questioned by a number of investigators. Thus Schonell (1940, 1941) observed that many of his cases of specific dyslexia, particularly older ones, showed no tendency to reversal, and Gilkey and Parr (1944) have shown that, among normal schoolchildren, a tendency to reversal is not inconsistent with superior scholastic achievement. In the present study, the evidence does not confirm Orton's observations (1937, p. 151) that the number of errors by reversal tends to correlate with the individual amount of retardation in reading. In fact, only two cases (Nos. 4 and 8) showed reversals in the course of attempts at normal reading and writing ; five showed them only on a specially designed test ; and five showed no reversals at all, although two of these " reversed " the ambiguous figure. It seems that the tendency to reversal, although frequent, cannot be regarded as the cause of the difficulty in acquiring sequences. On the other

* Case 3 had also frank psychiatric symptoms, Case 7 had idiopathic epilepsy, and Case 12 a chronic left otitis and mastoiditis ; but none of these was considered a primary cause of the dyslexia.

hand, this tendency, and, in the present group of patients, perception of an ambiguous figure in a right-to-left direction, may be considered as an expression of this series-disability with material which may be seen in a right-left as well as a left-right direction: as far as direction of gaze is concerned, they may be said to be looking "at random." As the dyslexic grows older he may overcome this tendency to reversal, as Schonell has observed, but is left with a primary disability in acquiring sequences which hinders his acquisition of reading and writing.

At the same time the evidence from the Phi Test does not appear to support the second part of Orton's theory that specific dyslexia arises from "a confusion in cerebral dominance"; that these cases are ones "in whom the dominance for some functions is in one hemisphere and for some in the opposite" (1943). It has been demonstrated that in normal readers the perception of apparent movement is predominantly in the half-field of vision which is related to the dominant hemisphere; and, although it cannot be claimed that this perception be directly related to the ability of a hemisphere to acquire reading and writing patterns, the consistency of the observation, with right- and left-handed subjects, suggests that it is an expression of what Jasper termed "unilaterality in general neural organisation". If, then, dominance in cases of specific dyslexia were in fact established in the opposite hemisphere, it might be expected that apparent movement would be perceived in the opposite half-field; or were it "confused" or equally distributed in both hemispheres, the apparent movement might alternate (which it did in at the most three patients, Nos. 1, 2, and 5) or occur simultaneously in both directions (occasionally in Cases 6 and 11). The observation that in specific dyslexics, as in many of Jasper's stutterers, little or no apparent movement is perceived, suggests that in these patients the neurophysiological organization corresponding to "dominance" has not been established in a normal fashion in either hemisphere.

In conclusion, it must be emphasized that this study with the Phi Test can only be regarded as a preliminary approach to the question of hemispheral dominance in visual functions, and in association with reading disability. Even if no more effective indicator of cerebral dominance in these functions is evolved, a number of problems remains to be solved. Before an attempt can be made at answering the question of structural basis of this disability, Phi Test investigations will be needed of cases of acquired lesions and areas of dysfunction in the dominant hemisphere, and the relation of dominance to direction of gaze may require a study of subjects from cultures in which the reading-direction is from right to left.

Summary

By comparing the extent to which apparent movement is seen in the two half-fields of vision, Jasper and Raney's Phi Test enables an estimate to be made of hemispheral dominance in this function, and close agreement has been found between the hemisphere indicated on this test and that indicated by the subject's handedness.

Twelve cases of specific reading disability have been examined with this test: the noteworthy feature of their performance was that the majority of the patients reported little or no apparent movement (agreeing with Jasper's earlier experience with stutterers). The evidence from this test, and from the patients' performances in reading and writing, does not support Orton's theory that the basis of specific dyslexia is a "confusion in cerebral dominance", with failure to elide "antitropic records" in the minor hemisphere. It suggests rather that in these cases the neurophysiological organization corresponding to dominance has not been normally established in either hemisphere.

I am indebted to members of the staff of the National Hospital and to Drs. D. Whittaker and H. V. Dicks for permission to make reference to their cases, and to Professors R. C. Oldfield and O. L. Zangwill for their encouragement and advice.

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ELECTROMYOGRAPHIC AND ENDOCRINE STUDIES IN CHRONIC THYROTOXIC MYOPATHY

BY

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If the number of cases of a disease reported in the literature can be taken as an index of frequency, chronic thyrotoxic myopathy is a very rare disease. Its interest lies, however, not so much in its rarity as in the light it may throw on the inter-relationship of the endocrine glands and muscle function.

In a previous paper (Sanderson and Adey, 1949) some aspects of this problem were reviewed and a case was reported in which the electromyographic findings were those typical of muscle dystrophy. Two further cases are presented here with the electromyographic findings, and with investigation of the function of the adrenal cortex in one case.

The electromyograms give positive evidence of a muscular dystrophy of severe degree and show a return to the normal pattern after treatment of the thyrotoxicosis, thus making the diagnosis beyond doubt. The tests of adrenal cortical function were designed in rather a hurry and partly for this reason, but more especially because such tests are comparatively crude, the evidence for depressed function is inconclusive. That such a depression of function may occur in this disease is suggested by the necropsy findings of Thorn and Eder (1946) of atrophy of the glomerular layer of the adrenal cortex.

Case Reports

Case 1.—Mrs. M. C., aged 55, was admitted to the Royal Adelaide Hospital on July 8, 1949. At the age of 11 months she had suffered from infantile paralysis which had left the right arm and right leg weakened. However, she had always been active and done her own housework, and was married and had three children. Six months before admission she began to have shaking of the limbs and palpitation, and she became unduly excitable; she also noticed weakness of the limbs. The weakness progressed until at the time of admission she could not walk without support. She had lost 28 lb. in weight in the previous six months. The menopause occurred five years before.

Examination showed her to be very thin, weighing 74½ lb., with slightly staring eyes and a visible swelling of the neck. The thyroid gland was evenly enlarged, soft and smooth. The pulse rate was 90, the blood pressure 150/60 mm. of mercury. No abnormality was found on examination of the cardiovascular system, respiratory system, or the abdomen. There was considerable wasting and gross weakness of the muscles of the limbs. The muscles of the right upper arm, the flexors of the fingers on the right side, and the extensors of the right knee were much more severely affected than the rest of the limb muscles. Fasciculation was noted in the right quadriceps femoris muscle. The tendon reflexes were all present in the left arm, but those of the biceps and triceps brachii were absent in the right arm. The only reflex obtained in the legs was the right ankle jerk. The plantar responses were flexor. There was a fine tremor of the fingers. The urine was normal.

She was given an injection of 0·5 mg. of "prostigmin" on two occasions. She claimed that there was a definite increase in power after the first, but two days later there was no response. Her basal metabolic rate was +28%. An electromyogram from the left deltoid muscle was diagnostic of a myopathy and did not suggest the presence of a long-standing lower motor neuron lesion such as poliomyelitis.

After preparation with iodine, subtotal thyroidectomy was performed by Mr. Ian Hamilton. Histological examination of the gland showed hyperplasia and the formation of some papillary processes. Her convalescence was satisfactory and she was discharged showing some improvement in muscular power. A further electromyogram eight weeks after the first indicated that the myopathic process was still present but there was some evidence of recovery.

Her case was reviewed in August, 1951. She was then able to do her housework, and said that her muscular power and weight had returned to what they had been before her illness began. She was no longer excitable and was sleeping well. Examination showed no exophthalmos and no tremor, the pulse rate was 72, and there was a considerable increase in muscle bulk, even in those muscles previously affected by poliomyelitis. The muscular power was very much increased. Her weight was 100 lb. An electromyogram was not performed at this time.

Case 2.—E.B., a pensioner, 68 years old, was admitted to the Royal Adelaide Hospital on May 16, 1951. He complained of progressive weakness, muscular cramps,

loss of weight, and vomiting for six months. The loss of weight began 18 months before and at the time of admission amounted to 70 lb. Six months previously he began to notice difficulty in climbing stairs and in getting out of chairs, and about the same time he found that if he had to stand for any length of time he would vomit. The vomiting was preceded by nausea and related only to standing. He was not irritable and did not sweat excessively. He had disliked hot weather all his life and became very shaky at times. His appetite had always been good. At the time of admission he was very weak, but did not complain of fatiguability. He was suffering from muscular cramps at night. His relatives had noticed that his voice had altered. His previous illnesses were jaundice and trench fever in the 1914–18 war. He could give no details of family illnesses.

On examination he was a very thin and weakened elderly man with a mild degree of exophthalmos. The thyroid gland was smoothly and uniformly enlarged. The pulse rate was 96, the blood pressure 155/65 mm. of mercury. The cardiovascular and respiratory systems and the abdomen were normal. Rectal examination showed the prostate gland somewhat enlarged but normal in other respects. The testes were normal. Palmar erythema was present and there was a fine tremor of the fingers. The tongue was long and thin, and no fasciculation was noted ; the palate moved less than normal. His voice was gruff and had the windy quality that goes with palatal weakness. The vocal cords moved normally. There was a generalized gross muscle wasting affecting the roots of the limbs somewhat more than the extremities, and this was accompanied by very considerable weakness, especially of the triceps brachii and quadriceps femoris muscles. Occasional fascicular twitching was seen in the triceps, quadriceps, and interossei muscles of the hands. Tendon jerks were all present, equal, but less active than normal. The plantar responses were flexor and the abdominal reflexes were present. The urine was normal. His weight was 104 lb. His sleeping pulse rate varied from 84 to 96.

Special Investigations.—The only abnormality found by haematological examination was a mild degree of anaemia (haemoglobin 11·3 g.%). The blood urea was 28 mg.%, the serum electrolyte levels were sodium 140 m.Eq/litre (method of Noyons), potassium 5·1 m.Eq/litre (method of Abul Fadl), and chloride 108 m.Eq/litre. The B.M.R. was +30%. No abnormality was found on radiological examination of the chest or by an opaque meal, but examination of the spine, pelvis, and femora revealed severe osteoporosis. An electrocardiogram showed the S–T segment down-sloping in leads 2, 3 and V6, and the T waves low or diphasic in these leads suggesting myocardial disorder or damage. A tracing after two weeks' treatment was normal. Tests of liver function were normal. A glucose tolerance test gave the following levels : fasting 0·09 g.%, half an hour after 50 g. glucose 0·16 g.%, one hour 0·11 g.%, one and a half hours 0·08 g.%, two hours 0·07 g.% (Folin Wu method on venous blood). The Robinson-Power-Kepler test was positive on two occasions, the values for " A " being 4·9 and 8. The fall in eosinophils four hours after the injection of 0·3 mg. of adrenalin was 35% and after 25 mg. A.C.T.H. was 54%. The urinary excretion of 17-ketosteroids was 12·4 mg. in 24 hours, of creatine 0·008 g., and creatinine 0·68 g. The electromyographic findings are discussed below.

Treatment and Course.—Treatment with methyl thiouracil was begun on May 27, the dose being 200 mg. daily for four weeks, 100 mg. for a further four weeks, and 50 mg. daily thereafter. He was given a diet containing at least 200 g. of protein a day supplemented with vitamins of the B group parenterally. He improved steadily, gaining 10 lb. weight in the first four weeks. The sleeping pulse rate fell to below 80. The bulk and power of the muscles gradually increased, the palate regained full movement, and the exophthalmos disappeared. The patient was most gratified with his improvement, but complained of pains in the joints of the upper limbs. Three weeks after treatment was begun he developed peri-articular swelling and limited mobility of the finger joints. After eight weeks' treatment the B.M.R. had fallen to − 4% and the Robinson-Power-Kepler test gave a negative result. The patient continued to improve steadily, gaining in weight and strength, and was able to resume his normal activity. The symptoms of arthritis in the fingers and shoulders lessened during the fourth month of treatment, and when last reviewed on September 18 he had no peri-articular swelling, a full range of movements, and muscular power and development normal for a man of his age. He had not vomited and his weight was 160 lb.

Tests of Adrenal Function in Case 2

The serum electrolyte levels were all normal. The Robinson-Power-Kepler test, which was abnormal on two occasions before treatment was begun indicating impaired adrenal function, returned to normal after the thyrotoxicosis was controlled. The glucose tolerance curve was within normal limits. The urinary excretion of 17-ketosteroids was normal. The eosinophil response to adrenalin was 35% depression compared with the normal 50% or more (Recant, Hume, Forsham, and Thorn, 1950). The eosinophil response to A.C.T.H. was 54% depression, a normal result. Taken together these two responses suggest subnormal production of A.C.T.H. by the anterior pituitary causing adrenal insufficiency (Recant, Forsham, and Thorn, 1948).

During the first five weeks of treatment eosinophil counts were done by the method of Dunger on capillary blood, four days a week at 10 a.m. and 2 p.m. Every second day a subcutaneous injection of 0·3 mg. of adrenalin was given after the first specimen was taken, the other days being used as controls. During this period there was a conspicuous clinical improvement and it was hoped

TABLE I

PERCENTAGE ALTERATION IN CIRCULATING EOSINOPHILS

	1st Week	2nd Week	3rd Week	4th Week	5th Week	Mean
After 0·3 mg. adrenalin	−32 −36	−24 −26	−15 −31	−31 −33	−43 −29	−30 ± 2·42
Control	−18 −10	−26 +3	+15 +12	−8 −10	−4 +14	−3·2 ± 4·07

that the eosinophil response would show a corresponding temporal regression, indicating an improved adrenal function. The results are summarized in Table I.

The figures obtained were analysed statistically. No significant temporal regression could be demonstrated in this series, or in the absolute eosinophil counts from which it is derived. The mean of the control series did not differ significantly from 0. The mean of the adrenalin series was 30 ± 2·42% depression.

Periodic further adrenalin eosinophil responses remained subnormal, the last giving 44% depression on September 18.

Electromyographic Findings in Case 2

The electromyographic studies were carried out by inserting a concentric needle electrode into the right triceps muscle, which was fairly representative in its degree of wasting. The needle electrode was prepared by running an insulated wire through the shaft of a hypodermic needle. The end of this wire is bared and projects through the bevelled orifice of the needle. The sheath of the needle acts as a shield to the bared wire tip, which thus records the electrical activity only from motor units in the immediate vicinity of the needle tip (approximately for a distance of 0·5 cm.). Activity in individual motor units is thus easily recorded by means of a five-stage amplifier and twin-beam cathode-ray oscilloscope.

At the first examination on May 22, 1951, six days after admission to hospital, the number of motor units active during voluntary contraction of the right triceps muscle was considerably reduced, and the voltage from these units below normal. Fibrillation potentials, which would indicate some neurogenic lesion, were not seen when the muscle was at rest.

An analysis, after the method of Petersén and Kugelberg (1949), was made of the activity in 82 different motor units during voluntary contraction. The duration of these units is very greatly reduced from the normal 5–10 m.sec., with a preponderance in the range 2–4 m.sec. (Figs. 1 and 2). Statistical analysis shows a mean duration of 3·8 m.sec. A histogram from the normal biceps is presented for comparison. No action potentials with a duration longer than 11 m.sec. were seen, and all those longer than 6 m.sec. were highly polyphasic. These changes are diagnostic of a muscular dystrophy.

A further test on June 26, 1951, showed that there was still an undue proportion of action potentials in the range 4–6 m.sec. An appreciable number of spikes in the range 10–14 m.sec. had reappeared, but they were polyphasic in most cases. As in the previous test, no fibrillation potentials were seen at rest. The histogram of 82 different action potentials on this occasion shows an appreciable reversion to the normal type. The mean duration was 5·7 m.sec.

A third electromyograph on August 8, 1951, showed still further improvement, with considerably more action potentials in the range 10–17 m.sec. than at the time of the second test. However, persistent fast activity was still present in an appreciable number of motor units in the range 1–3 m.sec. The presence of numerous highly polyphasic units in this test made the interpretation difficult. The histogram was prepared from only 48 units. The mean was 6·2 m.sec.

A final examination on September 19, 1951, produced a histogram of 61 different motor units which is essentially that of a normal muscle. No action potentials with a duration of less than 3 m.sec. were seen, and the mean duration was 7·3 m.sec.

The electromyographic findings illustrated by the histograms were subjected to detailed statistical analysis and compared with the values given by Petersén and Kugelberg for the normal biceps muscle. These authors presented their results as a histogram, and from this the frequency distribution of action potential duration was reconstructed. It is possible that a little inaccuracy resulted here. However, the close correspondence of the mean and variance of the mean calculated from these figures with the values given by Petersén and Kugelberg show that any errors introduced by this procedure have been slight.

Table II gives the statistics of the distributions of the action potential duration (in milliseconds) of the four tracings we made in Case 2 and those computed from Petersén and Kugelberg.

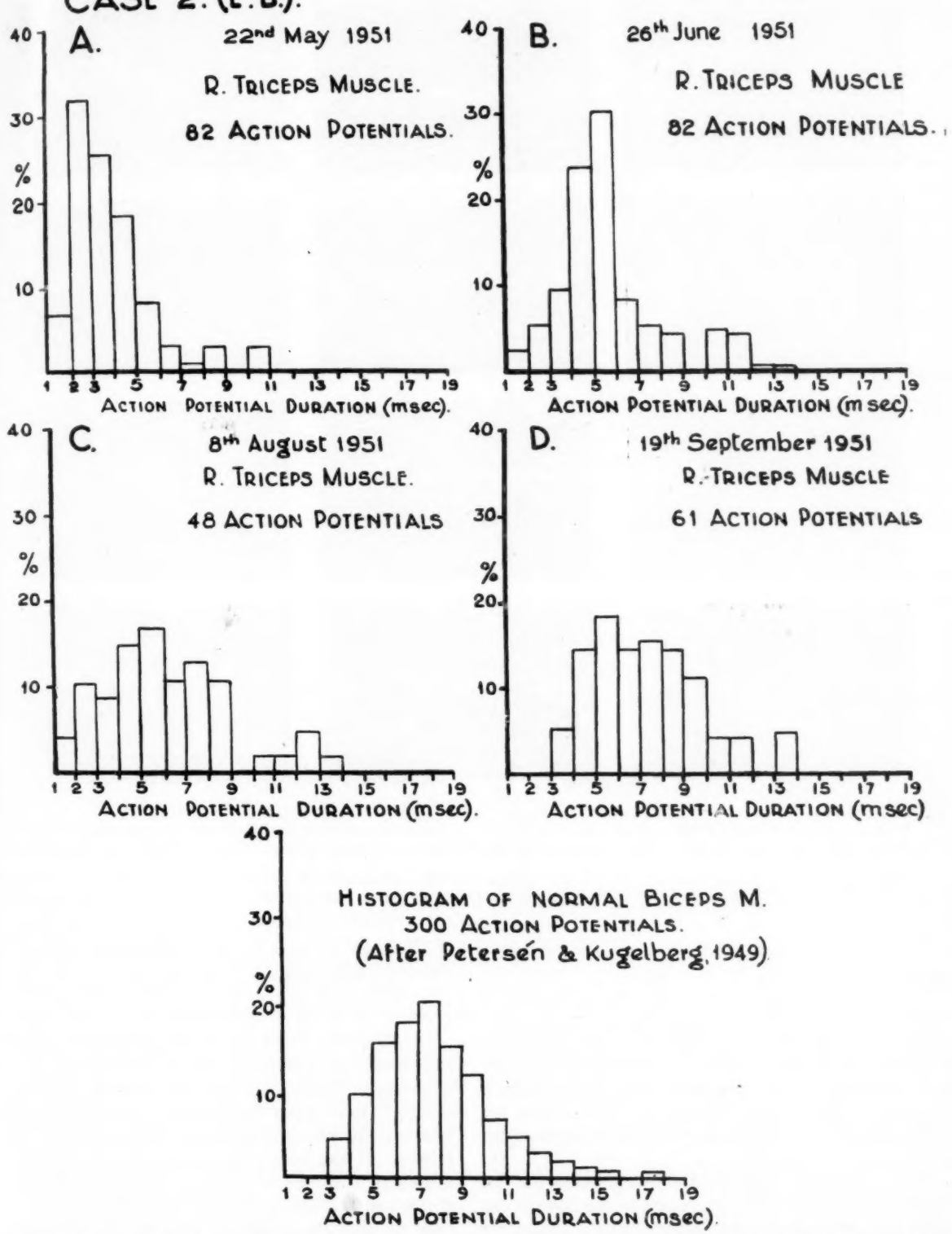

FIG. 1.—The histograms A, B, C, and D show clearly the great increase in action potentials of short duration (2–4 m.sec.) in the right triceps muscle at the onset of treatment (A) and the gradual recovery of a normal distribution with a mean in the vicinity of 7 m.sec. (D). At this stage no action potentials faster than 3 m.sec. were detected.

E

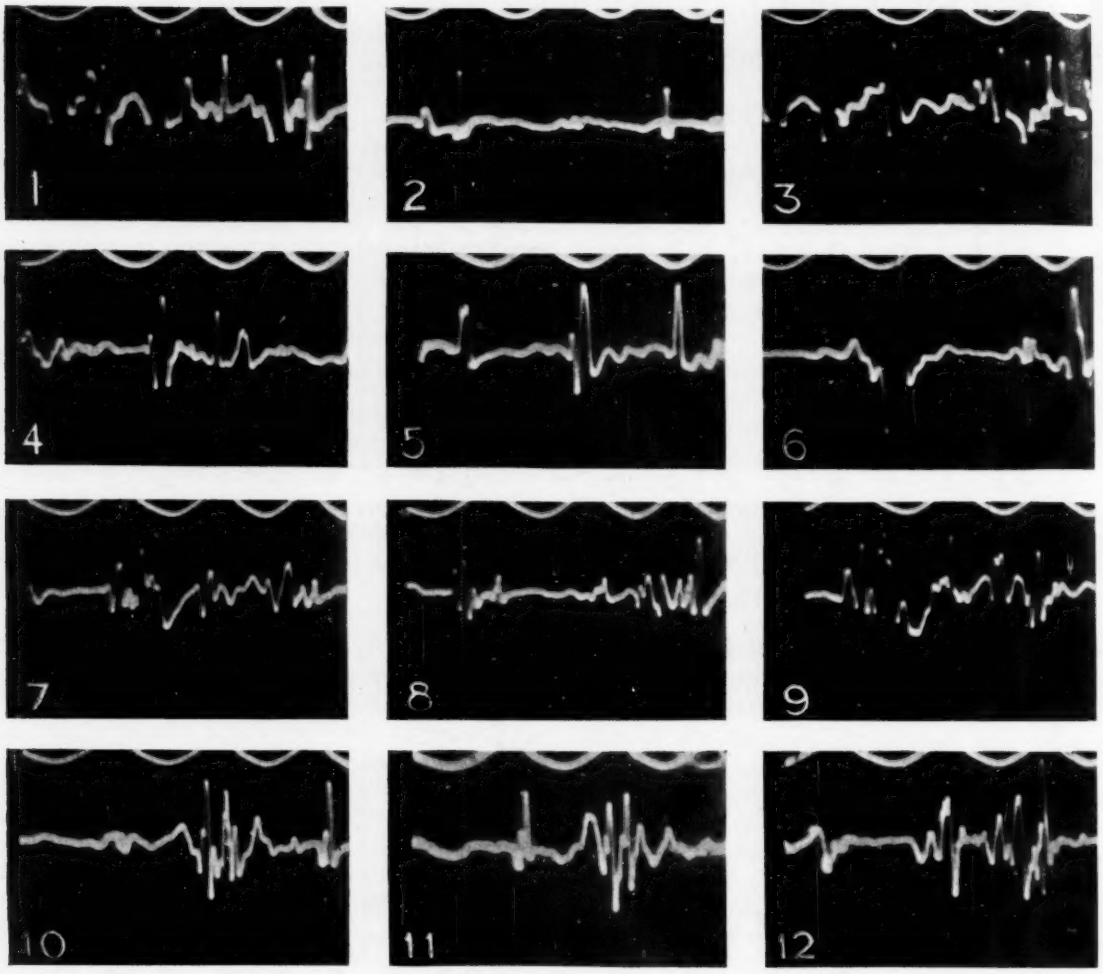

FIG. 2.—All tracings from the right triceps muscle. Time markers = 20 m.sec.
Tracings 1, 2, and 3 from the first electromyograph on May 22, 1951, showing numerous action potentials in the range 2–4 m.sec.
Tracings 4, 5, and 6 from the second electromyograph on June 26, 1951. The number of short duration potentials was less than at the first test.
Tracings 7, 8, and 9 from the third electromyograph on August 8, 1951. The mean duration at this test was 6·2 m.sec.
Tracings 10, 11, and 12 from the fourth electromyograph on September 19, 1951. Mean duration 7·3 m.sec.

The mean action potential duration shows a progressive increase from trace I to trace IV. When the difference between the various tracings is tested it is found to be highly significant between I and II, not significant between II and III, significant between III and IV, and not significant between IV and the normal. The value of trace III is lessened because of the smaller number of observations for comparison. The results of the tests of significance are shown in Table III.

This statistical analysis, therefore, confirms the impression gained from inspection of the histograms that the electromyogram taken before treatment was grossly abnormal, and that those taken during the course of treatment progressively improved, the last tracing being almost normal.

Discussion

Our knowledge of chronic thyrotoxic myopathy has been adequately reviewed in the papers of Brain and Turnbull (1938), McEachern and Ross (1942), Thorn and Eder (1946), Devic, Froment, Guinet, and Devic (1947) and Sanderson and Adey (1949). It has been postulated that the thyrotoxic muscular disorders result from the action of several endocrine factors on striated muscle and that the type of disorder produced depends on the pattern of endocrine disturbance. However, the nature of

TABLE II
DISTRIBUTION OF ACTION POTENTIAL DURATION

	Trace I	Trace II	Trace III	Trace IV	Normal
No. of observations	82	82	48	61	300
Mean	3·80	5·73	6·21	7·27	7·59
Variance	3·3010	6·1061	8·9770	6·0802	5·9578
Variance of the mean	0·0403	0·0745	0·1870	0·1013	0·0199
g_1	1·6966	1·2011	0·7052	0·7413	0·9009
g_2	3·7043	1·4413	0·1018	0·2623	1·4489

TABLE III
RESULTS OF TESTS OF SIGNIFICANCE

Testing Difference between Means	S.N.D.*	P†
Trace I and II	5·687	<·001
Trace II and III	0·932	·35
Trace III and IV	1·971	<·05
Trace II and normal	6·060	<·001
Trace III and normal ..	3·045	<·01
Trace IV and normal ..	0·938	·35

*Standard normal deviation. †The probability that the difference is due to the action of chance.

the interaction of the thyroid with other endocrine glands is still imperfectly understood, and the reason why on very rare occasions a patient with thyrotoxicosis develops severe myopathy or myasthenia gravis is completely obscure. The importance of chronic thyrotoxic myopathy, from the viewpoint of experimental medicine therefore, is that there is an inter-related disturbance of thyroid and muscle function, probably mediated by the anterior pituitary-adrenal system which can be varied at will by the use of antithyroid drugs. It seems likely that a close study of these patients would add to our knowledge of this still obscure branch of endocrinology.

The present electromyographic observations confirm and amplify those we previously reported. After the patient is treated the return to the normal pattern appears to take two or three months. The comparison of serial tracings is made more precise by the analysis of action potential duration.

Our findings support the suspicion that adrenal function is depressed in this disease. In our experience the eosinophil response test is not so sensitive or accurate a measure of adrenal function as some reports have suggested, and the Robinson-Power-Kepler test is the most sensitive test available. In the related condition of myasthenia gravis and malignant exophthalmos Zondek and Ticho (1951) have reported a positive Robinson-Power-Kepler test which became normal after treatment.

Summary

Two further cases of chronic thyrotoxic myopathy are reported. The electromyographic findings in one case are illustrated and described. These were diagnostic of myopathy and returned to the normal pattern after control of the thyrotoxicosis. Statistical analysis of the duration of the motor unit action potentials has been used to assess the change.

Tests of the function of the adrenal cortex on one patient gave inconclusive results. Serial estimations of the eosinophil depression in response to adrenalin showed no change during the first five weeks of treatment with thiouracil. The Robinson-Power-Kepler test, positive before treatment, became normal after the thyrotoxicosis was controlled. The eosinophil response was still subnormal after four months' treatment although the patient appeared to have recovered completely.

The authors are indebted to the Board of Management of the Royal Adelaide Hospital and to Drs. Guy Lendon and J. G. Sleeman for permission to report the two cases, and to Professor A. A. Abbie, Department of Anatomy, University of Adelaide, for the facilities to perform the electromyograms. Dr. E. A. Cornish of the Commonwealth Scientific and Industrial Research Organisation gave much assistance by carrying out the statistical analyses. The special investigations were performed by members of the staff of the Institute of Medical and Veterinary Science, Adelaide.

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OBSERVATIONS ON A CASE OF MYOTONIA PARADOXA

BY

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Myotonia, the phenomenon of prolonged after-contraction of a muscle after voluntary effort has ceased, is seen in several conditions of which the commonest are dystrophia myotonica (myotonia atrophica) and myotonia congenita (Thomsen's disease). A rarer manifestation is that designated as paramyotonia in which the myotonia appears only with cold or less usually with heat, while rarest of all is myotonia paradoxa. Whereas in ordinary myotonia the initial movements are most hampered and continued use of the muscle relieves the myotonia, in myotonia paradoxa the myotonia increases with activity until movement may be completely arrested. Maas and Paterson (1950) mention a few authors who have observed this phenomenon. Franceschetti, Klein, and Walthard (1947) quote Curschmann as saying that ordinary myotonia may be found in one group of muscles with myotonia paradoxa in another group in the same patient. The second case described by Franceschetti and others (1947) was one of myotonia in the arms on initial movement, but when the patient came to climb the stairs the myotonia in the legs became progressively worse. The present case was unusual in showing myotonia paradoxa in pure form. Never at any time during daily observation for many weeks was myotonia present on initial movement, nor could the patient recollect such an occurrence at any time in his life. Initial movements were always unencumbered but as movement progressed myotonia developed and increased until he was incapable of further movement.

Case Report

The patient was a man aged 21 years. His father and mother were both alive and well and had never suffered from any muscular disability. His father went bald as a young man and his paternal grandfather had a cataract. A female second cousin of the patient's mother had suffered from some muscular disease, but its nature was unknown and efforts to trace her failed. He had one sister three years older than himself who was in good health.

The patient could carry his earliest recollection of his disability back to the age of 4 years when it was noticed that he lagged behind his parents when walking because of which they used to chide him. When he started school this disability became more noticeable as he could not keep up with other boys. He was referred to the School Medical Officer and was excused games and physical training. About 13 years of age he became more aware of the nature of his trouble, for after hanging from a horizontal bar by his hands he found that they became weak and powerless while his fingers remained flexed and defied his efforts to extend them voluntarily. This was accompanied by a "knotted feeling" in the bellies of the muscles in the forearm which lasted several minutes, after which the fingers gradually relaxed and the power returned. After leaving school he began work as a draughtsman and, though long-continued drawing would bring on the loss of power in the fingers, he was able to continue his work by means of suitable respites. He was called for National Service and passed through his basic training by being excused drill and parades. Subsequently he continued work as a draughtsman in the Royal Engineers but was never able to do drill, and so he was referred to hospital.

He described his difficulty well and clearly. Whenever he began to use a muscle or group of muscles the initial movements were free and powerful. With continued exercise, however, there first appeared a dull ache followed quickly by a progressive loss of power in the muscle accompanied by a tight, knotted feeling in its belly. This rapidly led to complete loss of power, the muscle remaining in the shortened position. When he felt the muscle belly at this point it was hard and board-like. After resting a few minutes the muscle gradually relaxed, its belly became soft, and the power returned. If he exercised the muscle more quickly or against a greater resistance the weakness came sooner. By keeping the rate of exercise below a critical level, as for instance in walking slowly, he could avoid the loss of power indefinitely. Rapid walking or walking up steep hills would quickly bring it on. The trouble was worse when he was cold or very hot or when hungry. General bodily fatigue might make the weakness appear more rapidly in a particular group of muscles, but he had not noticed any tendency for it to be worse towards the end of the day. It affected all limb and trunk muscles and also the muscles of mastication and deglutition. He had never noticed any diplopia nor ptosis.

Also he had noticed for several years that occasionally

when using a muscle it would begin to tighten and weaken as usual and then, though activity was continued, the symptoms subsided and he could then continue to use the muscle indefinitely. This he had named his "second-wind".

He was 5 ft. 9 in. (175 cm.) tall and weighed 146 lb. (66 kg.). His hair was receding from his forehead and was a little thin over the vertex. The distribution of body hair was normal. The heart, lungs, and abdomen showed no abnormality, and there was no testicular atrophy. In the central nervous system fundi, pupillary reactions, and cranial nerves were all normal. Deep tendon reflexes were active and equal, abdominal reflexes were present, and the plantar responses were flexor. Sensation and coordination were intact.

Muscular development was good, but there was no suggestion of hypertrophy on the one hand nor of atrophy on the other, and the muscles at rest were normal to palpation. There was no disturbance of tone nor was any fasciculation seen. Percussion of the muscles failed to produce a myotonic response. Power, when tested conventionally by using a muscle once or twice against resistance, was normal in all groups of muscles. When a muscle was tested continuously, as for example the biceps brachii by repeatedly flexing the elbow against resistance, the initial movements were powerful, but gradually the power decreased until he would be completely unable to flex the elbow even against gravity. Simultaneously the belly of the biceps was felt to be hard and board-like. This condition persisted from one to three minutes and then gradually passed off as the power returned. In the case of the long flexors of the fingers the hardening of the muscles was accompanied by a shortening which left the fingers in a flexed position.

The serum calcium level was 10·4 mg. per 100 ml. and serum potassium 17·6 mg. per 100 ml.

Experiments

The muscle tests in the following experiments were done as follows.

Quadriceps.—The patient sat on a table with the thighs horizontal and the lower leg hanging vertically downwards over the edge. A loop, carrying a 6 lb. weight, was placed over the dorsum of the foot. The patient raised the lower leg to the horizontal by extending the knee and lowered it again at the rate of once every two seconds. The result was scored as the number of times the leg was raised before it failed to reach the horizontal level.

Biceps.—The supinated forearm was laid on the table with a 7 lb. weight in the hand. The forearm was raised to the vertical by flexing the elbow and then lowered at a rate of once every two seconds. The result was scored as the number of times the forearm was raised before it failed to reach the vertical.

Index.—The supinated forearm was laid on the table and a loop was placed over the terminal phalanx of the index finger. The loop was attached to a string which passed over a pulley to be attached to a 2 lb. weight. The index finger was flexed fully at the proximal interphalangeal joint and then extended. The result was scored as the number of times it was flexed before it failed to reach full flexion.

It should be noted that in every instance the failure to complete the contraction was not due to simple fatigue but to the development of myotonia.

Experiment 1: Comparison of Patient with Normal Control.—The power of the patient was compared with a normal control of similar height, weight, and muscular development (Table I), and was found to be greatly impaired by the development of myotonia. This comparison shows clearly how severely the patient was handicapped by his disability.

TABLE I

NUMBER OF MUSCULAR CONTRACTIONS BEFORE FAILURE COMPARED WITH A NORMAL SUBJECT

Muscle	Patient	Control
Right quadriceps	51	150
Left quadriceps	45	150
Right biceps	54	150
Left biceps	75	150
Right index	19	50
Left index	23	50

Experiment 2: Effect of Hunger and Food.—The patient had no food or drink from 8 p.m. to 9.30 a.m. of the following day. At this time the blood-sugar was measured (95 mg. per 100 ml.) and the muscular power was tested. He was then given 100 g. of glucose in water and a large breakfast, then at 11 a.m. the muscular power was re-tested. The blood sugar was then 130 mg. per 100 ml. The results are recorded in Table II and it appears that depriving the patient of food overnight did not enable the myotonia to be induced more easily. However, after the patient had been given breakfast

TABLE II

NUMBER OF MUSCULAR CONTRACTIONS REQUIRED TO PRODUCE MYOTONIA BEFORE AND AFTER FOOD

Muscle	Fasting	After Breakfast
Right quadriceps	56	84
Left quadriceps	64	74
Right biceps	51	152*
Left biceps	56	150*
Right index	14	22
Left index	17	21

* In both these instances the patient developed his "second wind" and was still going strongly when stopped at 152 and 150.

and the blood sugar had risen from 95 to 130 mg. there was a slight improvement in performance.

Experiment 3 : Effect of Repeated Testing.—The results of repeated testing of a muscle were observed by testing " the index " to the point of failure at 5-minute intervals. The results in Table III show that recurrent use of a muscle at short intervals did not aggravate the myotonia, which fact was supported by the clinical observation that the patient was not worse towards the end of the day.

TABLE III

EFFECT OF REPEATED TESTING ON NUMBER OF MUSCULAR CONTRACTIONS REQUIRED TO PRODUCE MYOTONIA

Time	Zero	5 minutes	10 minutes
Right index	11	9	13
Left index	12	8	13

Experiment 4 : Effect of Temperature.—The effects of temperature were observed by immersing the hand and forearm in a bath of water or melting ice at 1° C., 9° C., 15° C., and 41°C. for five minutes each. This alteration of temperature as shown in Table IV did not produce any great effect, though the patient had considered his trouble to be somewhat worse in extreme heat or cold. This is in contrast to paramyotonia where the myotonia develops only in the cold.

TABLE IV

EFFECT OF TEMPERATURE ON NUMBER OF MUSCULAR CONTRACTIONS REQUIRED TO PRODUCE MYOTONIA

Temperature	1°C.	9°C.	15°C.	41°C.
Right index ..	15	19	18	21
Left index ..	19	16	15	23

Experiment 5 : Effect of Ischaemia.—The effects of ischaemia were observed as follows. A sphygmomanometer cuff was placed round the right upper arm and inflated to 200 mm. Hg. The index was then tested and gave a score of 17 on the right. The left index was tested without ischaemia and gave a score of 18. After the point of failure of the right index had been reached the ischaemia was maintained. In contrast to the non-ischaemic experiments the hardness of the muscle belly and the continued flexion of the index finger did not subside after about one minute but remained unaltered for five minutes when the cuff was released. At another experiment a cuff was placed round the right upper arm and inflated to 200 mm. Hg. The limb was kept at rest and ischaemic paraesthesiae developed as usual. At the end of 20 minutes' occlusion there was no spontaneous hardening of the muscle. The right " index " was then tested and a reading of 18 was obtained before failure. The cuff was released immediately after the point of failure and the myotonia and weakness disappeared.

These observations on the effect of ischaemia were of great interest. Exercising the muscle during ischaemia did not induce myotonia any more quickly than when a free blood supply was available. However, once the myotonia was induced it did not disappear until the blood supply was restored. Ischaemia in a resting muscle did not induce myotonia, nor did exercise of the muscle after 20 minutes' ischaemia produce more rapid myotonia. These findings suggest that the changes brought about by muscular activity can only be reversed by a free blood supply but that ischaemia, in itself, is insufficient to produce the myotonia, muscular contraction being essential.

Experiment 6 : Effect of Isometric Contraction.—The effect of isometric contraction was tried by attaching the loop round the index finger to an immovable weight. The patient then tried to flex the finger as before. In the right hand 30 flexion attempts were made before myotonia developed, and in the left 18. There did not appear to be any difference, therefore, between isotonic and isometric contraction.

Experiment 7 : Effect of Faradic and Galvanic Currents.—Contractions induced by faradic and galvanic currents were observed. The right flexor carpi ulnaris was stimulated by a faradic coil at the rate of 30 contractions per minute. The contractions started strongly, began to fade after 15, and were a mere flicker at 25. The normal control was still contracting strongly after 100 contractions. On the left the contraction began to fade at 25 and was a flicker by 40.

When tested by a 9 milliamp galvanic current produced by a mechanical interrupter at the rate of 30 contractions per minute the flexors carpi ulnaris right and left were still contracting strongly at 60 and 90 respectively. This repeated observation was of considerable interest. The myotonic response to electrical stimulation was not seen, which was in line with the failure of mechanical percussion of the muscle to produce myotonia. Repeated faradic stimulation, however, caused development of myotonia and rapid loss of power. The galvanic stimulation, on the other hand, entirely failed to do this, nor did it, as in two cases of dystrophia myo-

tonica described by Adie and Greenfield (1923), produce a sustained contraction as long as the current was passing. Faradic current with its short pulses is unable to stimulate muscle fibres directly but acts through the motor nerve. Galvanic current, on the other hand, can stimulate muscle directly. The results of experiment 7, therefore, might suggest that the myoneural junction was involved in the development of the myotonia. This conclusion, however, is not justifiable, as the faradic current may have resulted in the muscle doing more work than when stimulated by galvanic current. The work done by the muscle under these conditions was unfortunately not tested.

An electromyographic examination was made of the forearm muscles with concentric needle electrodes. Insertion of the needle was followed by a tremendous outburst of electrical activity outlasting movement of the needle by many seconds as described by Brown and Harvey (1939) in congenital myotonia in goats. Voluntary contraction of the muscle was accompanied by action potentials which ceased as the muscle relaxed. With repeated contractions the myotonia gradually developed and was accompanied by the typical after-discharge. These electromyographic findings were very similar to those described by Brown and Harvey (1939).

Experiment 8 : Effect of Potassium Chloride.—The serum potassium level of this patient was 17·6 mg. per 100 ml. He was given 5 g. of potassium chloride in water to drink, and one hour later the muscle tests were performed (Table V), but there did not appear to be any aggravation of the myotonia. He was later given 45 gr. of potassium chloride daily and muscle tests were recorded on the third and twelfth days (Table V), again without any change being apparent.

TABLE V

EFFECT OF POTASSIUM CHLORIDE, QUININE, AND PROSTIGMINE ON NUMBER OF MUSCULAR CONTRACTIONS REQUIRED TO PRODUCE MYOTONIA

Muscle	K.Cl. (5 g.)	Third Day of 45 gr. K.Cl. per Day	Twelfth Day of 45 gr. K.Cl. per Day	Fifth Day of 45 gr. Quinine H.Cl. per Day	Third Day of 120 mg. Prostigmine per Day
Right quadriceps	—	31	41	—	—
Left quadriceps	—	38	44	—	—
Right biceps	37	28	31	34	36
Left biceps	32	30	29	25	19
Right index	13	17	22	18	21
Left index	15	12	21	19	21

Experiment 9 : Effect of Quinine Hydrochloride.—The patient was given 15 gr. of quinine hydrochloride three times a day for four days and on the fifth day the muscle power was tested (Table V), but there was no alleviation of the myotonia in contrast to the relief usually given by quinine in ordinary myotonia.

Experiment 10 : Effects of Prostigmine.—The patient was given 30 mg. of prostigmine by mouth every four hours from 6 a.m. to 6 p.m. daily. On the third day of this regime the muscle power was tested (Table V), no change as a result of the prostigmine being observed. Thus, in contrast to the findings of Russell and Stedman (1936) in cases of myotonia congenita, neither potassium chloride nor prostigmine aggravated the myotonia in this case.

Experiment 11 : Effect of Acetyl Choline.—Acetyl choline, 40 mg., was injected into the right brachial artery at the elbow (Lanari, 1937). A marked flush and profuse sweating appeared over the hand and forearm with slight weakness of the grip, as is described by Harvey, Lilienthal, and Talbot (1941). The power of flexion of the fingers was then tested simultaneously in both hands against an unknown resistance. Twelve contractions were obtained on the right against 24 on the left, while the degree of myotonia on the right was much more severe than that on the left.

Discussion

The most noticeable feature of this case was the complete absence of any suggestion of myotonia after the first few contractions. Though the patient was examined on numerous occasions over several weeks never once was myotonia on initial movement or a myotonic response to mechanical stimulation observed. The degree of disability on continued exercise of a muscle, however, was severe.

Opinion has differed as to the site of the lesion in myotonia. Russell and Stedman (1936) considered the lesion to be an excess of acetyl choline at the myoneural junction. Brown and Harvey (1939), who observed congenital myotonia in goats, thought that there was an abnormality of some part of the muscle fibre itself because they found the myotonia to be unaltered after severance and degeneration of the motor nerve and after curare. Denny-Brown and Nevin (1941) believed that there were two factors, a peripheral myotonia due to an abnormality of the muscle fibre, which in turn reflexly stimulated an " after-spasm " due to impulses from the motor nerve. The features of these two types of myotonia were not observed in this case. The observations made on this case have failed to throw much light on the problem of the site of the lesion.

The failure of quinine hydrochloride, potassium chloride, and prostigmine to influence the myotonia is strong evidence against the myoneural junction being at fault. Nor does the aggravation of the myotonia by acetyl choline contravert this, for, as acetyl choline causes contraction of muscle and the myotonia here developed with muscular contraction, acetyl choline would clearly increase the myotonia. The possibility that the myotonia was central and not peripheral is thus raised. A myotonia of central origin would differ from the " after-spasm " of Denny-Brown and Nevin (1941) in not being dependent on an initial peripheral factor. A central origin of the myotonia could only be proved by denervating or fully curarizing a muscle, which is, unfortunately, not possible.

Comparison of this case with other reports is, however, rendered difficult by the uncertainty as to whether the various forms of myotonia are but variants of the same condition or whether they are separate entities. Maas and Paterson (1939, 1943, 1950) from their extensive clinical and genetic studies believe that all forms of myotonia are manifestations of a unitary disease. Bell (1948) and Franceschetti, Klein, and Walthard (1947), however, oppose this view. The complete failure of potassium and prostigmine to aggravate the myotonia in this case or of quinine to relieve it, suggest fundamental differences from myotonia as seen in myotonia congenita and myotonia atrophica. From the clinical standpoint also so pure a case of myotonia strictly related to continued exertion does not appear to have been described. The possibility that the myotonia is in reality a form of muscle cramp seems unlikely in view of the constant, widespread involvement of all muscles, including the tongue and muscles of deglutition. It may well be that this form of myotonia paradoxa is essentially different from ordinary myotonia. Further observations on more cases are required to elucidate the problems which this case has presented.

Summary

A case of myotonia, entirely related to repeated use of a muscle (myotonia paradoxa) is described, and the results of several observations on the case are reported.

The implications of the observations are discussed.

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THE VITAL STAINING OF MUSCLE BIOPSIES WITH METHYLENE BLUE

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The histological changes of muscle occurring in neuromuscular diseases are often non-specific. They do not always enable us to find out the cause of an atrophy or a degeneration or to assess the part played by a disorder of innervation. Therefore, it would be desirable, when investigating muscle samples taken by biopsy, to be able to study systematically and simultaneously the muscular tissue and the nerve fibres and endings by special staining of axis cylinders and myelin.

The study of biopsies of nerve supply meets two difficulties: (1) the very unequal distribution of nerve endings in various parts of a muscle, so that it is never certain whether a biopsy taken at random will contain any; (2) the impossibility of getting an idea of the whole innervation of a muscle fragment by silver impregnation methods. Even if a selective and regular impregnation is obtained, and a great number of sections examined, it remains difficult with these methods to decide whether a biopsy contains any nerve endings and fibres, and to learn to recognize their appearance and distribution. Using Holmes' silver on the slide method systematically, I found that the probability of finding some nerve elements in a section of biopsy muscle was very slight. The first step to increase the probability would be to make certain that we obtained neuromuscular biopsies, that is, samples taken from areas of muscle containing abundant nervous elements. Such favourable areas could be mapped out if we were to use a histological method by which the richness in nervous elements of the biopsy tissue could easily be demonstrated. It was with this end in view that I became interested in the use of vital methylene blue.

The classical technique of vital staining in animals consists in perfusing the whole organism with a methylene blue solution, afterwards removing those organs of which the innervation is to be studied (Ehrlich, 1885-86; Dogiel, 1890). Hines and Tower (1928) used this perfusion method in their studies on the innervation of skeletal muscles of the cat. Another procedure is the local injection of the stain, and the subsequent removal of the stained material. Weddell (1941a and b) was able to observe the nerve endings in the skin by this method. I have used a similar method to obtain vital staining of neuromuscular biopsies, and, to the best of my knowledge, this technique of local injection of methylene blue has never been applied to the study of muscular innervation in man. It has proved satisfactory for this purpose, and it is hoped that it may be of some help to those working on muscle biopsies, who have often been discouraged by the difficulty of staining and finding nerve endings in this material.

In this preliminary paper only the technique and the interpretation of the pictures obtained are discussed. However, it is necessary to point out that most of the biopsies upon which this study is based were taken at the " motor point " which was localized, whenever possible, with threshold electrical stimuli. As a rule, the motor point corresponds with the spot where the nerve enters the muscle. It is reasonable to think *a priori* that there are more chances of finding nerve endings at this place than in an unexcitable part.

Material

The 31 biopsies at my disposal were taken from various muscles of the superior and inferior limbs: the deltoid, biceps, brachio-radialis, flexor carpi radialis, quadriceps, tibialis anterior, peroneus longus, gastrocnemius; the sterno-cleido-mastoideus, and abducens digiti quinti were each used once.

The patients were affected with either neuromuscular disorders, or primary muscular dystrophies or with systemic diseases in which muscle biopsy might help in diagnosis.

I shall avoid discussing the pictures observed from a physio-pathological point of view, especially since most of the appearances described were

found in muscles, of which the innervation could be considered normal.

Technique

After incising the skin and fascia under local anaesthesia with xylocaine without adrenalin, a fragment of muscle is removed for routine biopsy. Then an untouched bundle is selected and treated in the following way. With a thin needle (for intradermal injection) the muscle is infiltrated with an 0·02–0·03% methylene blue solution, proceeding as for an anaesthetic infiltration in order to produce regular staining. The solution is made up from sterilized 1% methylene blue diluted in the appropriate amount of normal saline. The stain is allowed to operate for five to 10 minutes, when the stained bundle is removed (about 1 c.cm. of muscle tissue) in two or three pieces. It is well known that parenteral methylene blue is harmless. I have never observed any unpleasant reaction following the injection. However, it is to be noticed that the muscle tissue when infiltrated with methylene blue reacts poorly to mechanical stimuli (pinching, cutting).

The samples, moistened with normal saline, are left exposed to the air for from half an hour to one hour. (It seems better to leave them in an atmosphere of pure oxygen.) A darkening of the blue can be seen during this process. The samples are then fixed in a saturated solution of ammonium molybdate for 24 hours at 0°C., and washed in three changes of distilled water. Further complementary fixation in 10% neutral formalin takes three to five days. (Too long immersion in formalin may fade the staining of the nerve fibres.)

The fragments are then cut as frozen sections. Before putting them on the stage of the microtome a thin layer of ice is formed on it so that the whole biopsy may be cut without difficulty. Serial sections of 100 to 150μ are cut. All the sections are kept and mounted on albuminized slides. At this stage it is possible to counterstain the sections with 1% carmalum.

Finally the sections are immersed in 90% alcohol, absolute alcohol, and toluol as usual and mounted in a synthetic neutral medium (" harleco " synthetic resin). The staining obtained in this way is permanent. Some sections stained more than a year ago are not at all faded.

Results

The coloration is usually much more intense at the periphery of the biopsy. This fact is obviously the result of the more complete oxydation of the " leucoderivative " formed in the living tissue. This oxydation occurs only in the surface of the sample when exposed to air. Small bits of tissue have therefore more chance of being fully stained. Using pure oxygen instead, the staining goes deeper and is more regular.

Muscle Fibres.—These are usually stained very pale green or light blue at the periphery of the sections. The sarcolemmal nuclei are never visible, whatever the intensity of the staining. The sarcolemma is sometimes apparent as a thin, wavy blue band, darker than the muscle fibre.

Vascular Endothelia.—These are irregularly stained ; usually they are only discernible as an outlining of the capillaries at the periphery of the sections.

Stroma.—Collagen fibres and fat cells are usually little stained. They sometimes show a slight metachromasia. In strongly stained sections the elastic fibres are often well seen. The arteriolar elastic laminae are also well stained.

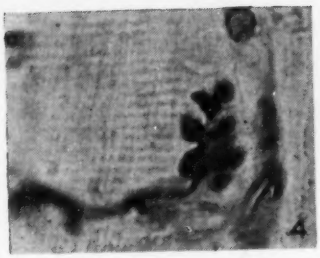
Nerve Fibres.—These are always the most deeply stained elements. They are always easily recognized amongst the other structures. Even when nothing else is stained, they may often be clearly followed up to their last ramifications. For the axis cylinders as well as for vascular endothelium the oxydation of the section by pure oxygen certainly gives more regular staining.

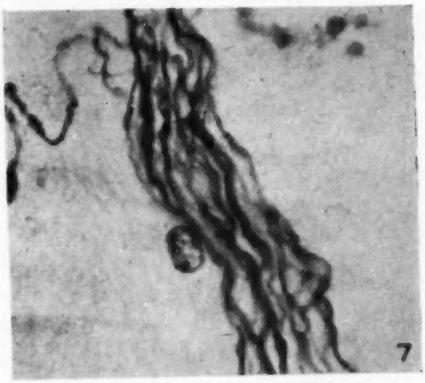
It is rather uncommon for nerve fibres not to be stained at all. Nevertheless, this staining is far from homogeneous. Sometimes they are uniformly dark blue and their width more or less regular. More often one may observe a dark central filament surrounded by a sheath of irregular width, the staining of which is lighter and irregular. The central filament is frequently interrupted and sometimes replaced by dark blue granulations.

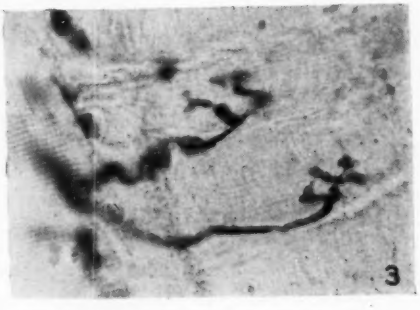
In the less stained preparations, the axis cylinder is uniformly pale blue with a darkening of the stain at the level of Ranvier's nodes where the axis cylinder becomes thinner (Fig. 8). Hence the whole appearance of the nerve fibre is that of a dotted line. Schwann and Henle nuclei are not visible. Myelin sheaths are sometimes apparent and show a metachromatic staining.

Nerve Endings.—My sections showed motor end-plates and muscle spindles.

Motor End-plates.—The nuclei of the sole are never visible. The cytoplasm of the sole can sometimes be distinguished from the rest of the muscular fibre by its lighter staining. This difference is more appreciable in deeply stained preparations (Fig. 5). The nervous arborization of the end-plate is easily demonstrated. It stains in a variable manner. As a rule the root of the arborization is deeply stained. One often finds the picture of a central filament surrounded by a paler sheath (Fig. 3). The branches of arborization are thin and less stained, and often end in an easily visible, club-like swelling frequently containing granules (Figs. 1 and







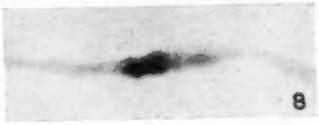


FIG. 1.—Usual aspect of motor end-plates in methylene blue preparation. The upper one is large. It shows the irregular staining of the arborization, the terminal swellings (which are few in this picture) being more deeply stained. At the bottom, a small end-plate is seen, slightly out of focus.

FIG. 2.—This is from a sample fixed in ammonium molybdate only. The transverse striation of the muscle is not visible. The axis cylinders are regularly stained. A triple motor end-plate can be seen.

FIG. 3.—Double motor end-plate. The dark-stained filament surrounded by a paler sheath is well seen on the root of the higher arborization. The granular structure of the endings is noticeable on the lower arborization.

FIG. 4.—Small end-plate resembling a bunch of grapes, because of its well-defined terminal swellings and contracted structure.

Fig. 5.—Strongly stained preparation. Nerve endings are broad. A central filament can be seen. This aspect resembles some of Couteaux's preparations.

FIG. 6.—Large end-plate without terminal enlargements. Compare with Fig. 4.

FIG. 7.—A nerve bundle showing how the axis cylinders usually stain.

FIG. 8.—A slightly stained axis cylinder, showing more intense coloration at Ranvier's narrowing. The narrowing of the axis cylinder can be seen.

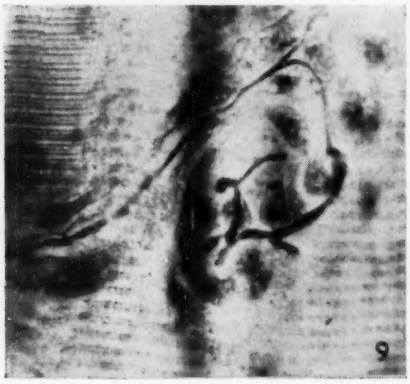


FIG. 9.—Aspect of a motor end-plate in silver impregnation (Holmes method). Compare the staining of the axon with methylene blue preparation.

FIG. 10.—Low magnification of a muscle spindle. Two motor end-plates on intrafusal fibres are visible.

FIG. 11.—High magnification of an intrafusal muscle fibre surrounded by an annulo-spiral nerve fibre.

3). Less often swellings are seen along the course of the fibres. When these terminal swellings are well formed, the arborizations resemble a bunch of grapes (Fig. 4). Only occasionally the width of the terminal branches remains regular and they do not end in a swelling (Fig. 6). Not only the shape, but also the size of these arborizations is quite variable and may differ in the proportion of 1 to 4. It must be pointed out that the best formed terminal dilatations are found in the smallest end-plates.

In some preparations I met with a picture that does not correspond with the classical description. The axis cylinder in the neighbourhood of a muscle fibre divides into two or three branches, each of which ends in a small arborization in the same muscle fibre, thus forming a double (Fig. 3) or triple (Fig. 2) motor end-plate.

Muscle Spindles.—In those parts of muscle rich in fibres and nerve endings, a muscle spindle can not infrequently be found. The nerve endings of these spindles are difficult to stain. They are only seen when the connective sheath has been torn by the needle during injection of the stain. In these more or less damaged spindles, where a haemorrhage is often found, the thin sensory fibres and the motor endings are easy to follow (Fig. 10). The latter are small and show beautiful terminal swellings. The annulo-spinal fibres and the thick axis cylinders from which they arise are usually pale blue and irregularly stained, and sometimes look like a string of beads.

It seems likely that the methylene blue enters the intact spindle only with difficulty, and that the tearing of the surrounding sheath is a necessary condition for the satisfactory staining of the nerve fibres.

Comments

Technique.—The optimal concentration of methylene blue appears to be between 0·02 and 0·03%. A higher concentration causes stronger impregnation of the muscle fibres, connective tissue, and elastic fibres, and lessens the contrast with the nerve fibres.

The time of staining of the muscle can be varied to some extent. Diffusion is rapid and the nerve structures are quickly impregnated. I believe that five minutes is long enough. After half an hour the staining of the infiltrated bundle fades and recoloration by exposure to air becomes difficult.

I tried to obtain staining by dipping a fragment of muscle in a dilute solution of methylene blue. The results were unsatisfactory. Only the most superficial parts were strongly and uniformly stained.

The time of exposure to oxygen is the most important part of the method. During this process the coloration becomes obviously darker. In order to obtain uniform staining, it is wise to treat small fragments of muscle. When the time of exposure to oxygen exceeds an hour, the recoloration becomes too strong. In particular, the vascular endothelia become very dark. Hence the wavy blood capillaries, which anastomose around the muscle fibres, are clearly distinguishable. Also the examination of nerve structures becomes difficult. Thirty to 40 minutes appears to be the optimal time. The action of ammonium molybdate is indispensable for the fixation and preservation of the stain.

I submit the specimens to a further fixation in formalin. This makes the pieces easier to cut, and shows up the muscular striation. In preparations cut after fixation with only ammonium molybdate the transverse striation is not visible (Fig. 2). The formalin tends to cause slight fading of the staining of the axis cylinders. Nevertheless, comparison with preparations untreated with formalin proves that this fixation does not alter the structure of fibres and nerve endings.

Results

The appearances of muscular nerve endings obtained with methylene blue have been thoroughly described by Dogiel (1890) and Tello (1944). The aspects we observed follow these descriptions fairly closely. They differ slightly from those given by silver impregnations in which the axis cylinder is usually stained homogeneously, and seldom show terminal swellings (cf. Fig. 9). Are these swellings part of the axis cylinder or of the *appareil sous-neural* (Couteaux, 1947), or do they represent the *gaine de l'arborisation* (Tello)? What I have been able to observe does not allow me to answer this question as yet. I have never been able to distinguish a sharp demarcation between the axonic thread and these dilatations, even in strongly stained preparations in which the terminal apparatus was particularly wide, and had some analogy with the structures described by Couteaux (Fig. 5).

I have not observed anything resembling Boeke's (1926) " periterminal network ". A sharp demarcation always exists between the axis cylinder and the motor end-plate within which it ramifies.

The most interesting observation to be drawn from my preparations is the marked polymorphism of the motor ending. This polymorphism does not appear clearly with silver impregnation, where there is rarely a chance to observe many motor end-plates side by side.

The size and form of the arborizations are most variable : the small motor end-plates usually contain short and thin ramifications ending in large swellings. In the larger end-plates the axonal arborizations are thicker and of more regular calibre ; terminal dilatations are less often observed. I found double or triple end-plates, which altogether make up a very large nerve ending. It is tempting to compare these structural differences with the appearances described by Carey (1941), but it is not my intention to discuss their functional significance as this author has done.

Conclusion

Vital staining with methylene blue can be used on biopsies of muscle. It easily gives results which are fairly reliable. This method is therefore of value for the evaluation of the richness in nervous elements of a muscle sample, and it may be used to map out the muscular territories which have the richest innervation.

The most interesting application of this method seems to be in studies on neuromuscular pathology.

Summary

A method of vital staining of muscle biopsies with methylene blue is described. A dilute solution of the stain is injected into the muscle to be examined. After removal, the sample is exposed to oxygen, then fixed in ammonium molybdate. After further fixation in formalin, the biopsy is cut in thick frozen sections, which are mounted in the usual way.

The results are described and their value discussed.

The polymorphism of motor end-plates shown by this method is emphasized.

I wish to thank Professor P. Gerard, in whose laboratory this work was performed, and Dr. J. G. Greenfield, who kindly helped me with the English translation and preparation of this paper.

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BOOK REVIEWS

(1) **The Croonian Lectures on Muscular Movements,** delivered before the Royal College of Physicians of London, June 1903, and (2) **Remarks on Paralysis of the Movements of the Trunk in Hemiplegia,** reprinted from the *British Medical Journal*, 1909, **I,** 881. By Charles Beevor; edited and reprinted for the guarantors of *Brain*. (Pp. 79. 5*s*.) London: Macmillan and Co. Ltd.

In issuing an inexpensive reprint of the "Croonian Lectures on Muscular Movements," delivered by the late Dr. Beevor in 1903, the guarantors of *Brain* have served medicine wisely. For this standard work, which is today so often praised, may in recent years have been less often read, and must certainly, on account of its inaccessibility, have been rarely owned by medical readers.

The lectures give an anatomical account of the simplest movements taking place at particular joints of arm, neck, and trunk; for example, flexion and extension at the wrist, pronation and supination of forearm. The muscle bellies taking part and their tendons were watched and felt, in paralysed as well as in healthy subjects. These methods are now, of course, in daily use in neurological and orthopaedic practice, and every medical student should become familiar with them during his study of human anatomy.

But the lectures are also a study in the physiology of willed movement, of which these simplest movements are examples. From this point of view, the modes of association of muscles acting about the joints are analysed. The order of recruitment of the muscles is described for movements of graded and measured power.

Most of the section dealing with problems of central representation has been omitted from the reprint "as containing views now no longer held". It will be generally allowed that cerebral localization is in many respects differently understood today than in 1903, and that this part of Lecture IV does not share the permanent value of the rest. Nevertheless, the deletion will be regretted by some. The modern experimental physiologist might be interested in Beevor's own appraisal of his work with Horsley, and in his discussion of the possibility that certain movement sequences are laid down in the spinal cord and are merely activated by cortico-spinal impulses. He is clear, at all events, that individual muscles are not accessible to the excitable cortex.

The Croonian Lectures are supplemented by a later paper, "Remarks on Paralysis of the Movements of the Trunk in Hemiplegia", in which is described a case of (presumed) capsular hemiplegia in which the patient, on trying to sit up, fell towards the paralysed side. A marvellous analysis of the disability is followed by an ingenious, but highly speculative, commentary.

The reprint is prefaced by a thoughtful foreword by Dr. Walshe.

Precepts and Counsels on Scientific Investigation. Stimulants of the Spirit. By S. Ramón y Cajal. Translated by J. M. Sanchez-Perez. Edited by C. B. Courville. (Pp. 180. No price.) Mountain View, Calif.: Pacific Press Publishing Association, 1951.

This essay was originally Dr. Cajal's address to the Royal Academy of Medicine, Madrid, in 1893. Since then it has been published in several Spanish editions and clearly must have been an inspiration to many research workers. It may at once be said that no intending research worker should fail to study the precepts and counsels set forth. The translation is good and the whole forms a delightful and fascinating account of this great scientist's thoughts on the life devoted to research. Dr. Cajal clearly had exceptional insight into the qualities and conflicts which existed in the minds of his junior colleagues, and his advice is amazingly practical. For example, he warns the beginner against excessive hero worship or devotion to *practical* sciences. Many types of investigator are criticized including the dilettantes or contemplators, the erudite or bibliophiles, the instrument addicts, and the constructors of theories. The environment favourable to scientific work receives special consideration and includes a thoughtful section on the investigator and his family. This even includes detailed advice as to the type of wife to choose.

Some of the comments are highly entertaining: "If our lips were not sealed by discretion we could illustrate these pages with vivid examples of how frivolously ostentatious tastes of the wife have interrupted brilliant careers, obliging the newcomer in science to exchange his study for politics, the microscope for the automobile, and the redeeming evenings in the laboratory for the useless hours spent at parties or in the theatre".

Die Nervenkrankheiten. By Georges Schaltenbrand. (Pp. 880; 539 figures. DM. 87.–) Stuttgart: Georg Thieme. 1951.

This textbook is an outstanding addition to neurological literature. It combines a remarkable thoroughness with a pleasant, interesting and up-to-date presentation of the subject matter. The author is clearly much more than a collector of information, and incorporates in his writing a thoughtful assessment of the facts. The several hundred illustrations are well chosen and clearly reproduced. There is a useful list of about 2,000 references divided according to subject. Neurologists will be well advised to add this important work to their library.

Livre Jubilaire. By the Groupement Belge d'Études oto-neuro-ophtalmologiques et neuro-chirurgicales. (Pp. 705 ; 126 figures and 21 plates. B.Fr. 350.–). Brussels : Journal Belge de Neurologie et de Psychiatrie. 1951.

The twenty-fifth anniversary of the foundation of the Groupement Belge d'Études oto-neuro-ophtalmologiques et neuro-chirurgicales has been marked by the publication of the proceedings of the meeting held in Brussels in September, 1950.

The theme of the session was a review of the vascular abnormalities affecting the central nervous system. The " Livre Jubilaire " contains nine excellent papers in which the clinical and pathological aspects of intracranial aneurysms and angiomas are discussed, and there is a section on the treatment of intracranial aneurysm. These are followed by a number of communications on the same subjects. Among the authors are some of the distinguished members of this society.

The majority of the illustrations are of an exceptionally fine quality and there are several good bibliographies. The volume provides a useful account of the subject.

Uber den Wahn. By Kurt Schneider. (Pp. 48. DM. 3.90.) Stuttgart : Georg Thieme. 1952.

This is an essay on fantasy, perception, and interpretation. The author makes a complicated distinction between fantasy or inspiration (*Wahneinfall*) on the one hand, and false interpretation of perceptions (*Wahnwahrnehmung*) on the other, and he maintains that false interpretation rather than perceptual disorder is at the basis of schizophrenia. He brings no new evidence to support his argument ; nor does he suggest how interpretation comes to be disturbed in the schizophrenic psychosis.

Theory of Mental Tests. By Harold Gulliksen. (Pp. 486. 48*s*.) New York : John Wiley & Sons, Inc.; London : Chapman & Hall. 1950.

In the introduction the author states his aim clearly : " this book deals with the mathematical theory and statistical methods used in interpreting test results ", but the actual contents might be more exactly described if the words " interpreting test results " were replaced by " manipulating normally distributed measures ".

Again, the author writes, " This book is written primarily for those working in test development ", and a student who is likely to become involved in large scale " objective " testing will indeed find interesting discussion, all the major techniques, many ingenious devices, and an extensive bibliography. On the other hand, practically everything which concerns the human being who takes a test is not within the scope of this book. The content or form of test items and all such contingencies as anxiety engendered by the examination, tensions at home or at school, recent removal from one town to another, or transient sickness lie outside the author's field and their effects in test results are not considered.

It may be no criticism of the book or the author to say that it could only thrive in an atmosphere of mass production. The expenditure of effort required to produce a fully " standardized ", " reliable ", " objective " examination can only be recouped on enormous groups of candidates or by tests remaining in service over a term of years.

A reader who wishes to learn about theories of mental testing will not find them here. He may not indeed find them easily elsewhwere, but there are a number of books, including some recently published such as " Mental Testing " by F. L. Goodenough or " Psychological Testing " by J. L. Mursell, which, though not dealing explicitly with theory, have much to say about the history, principles, and practice of the subject.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Die Vorträge der 2. Lindauer Psychotherapiewoche 1951. Edited by Ernst Speer. (Pp. 216. DM. 15.00.) Stuttgart : Georg Thieme. 1952.

Personality and the Frontal Lobes. (An investigation of the psychological effects of different types of leucotomy.) By Asenath Petrie. (Pp. 188. 21*s*.) London : Routledge and Kegan Paul. 1952.

Conditioned Reflex Therapy. The Direct Approach to the Reconstruction of Personality. By Andrew Salter. (Pp. 358. 20*s*.) London : George Allen and Unwin. 1952.

Diary of a Psychiatrist. By James T. Fisher, and Lowell S. Hawley. (Pp. 256. 16*s*.) London : Medical Publications Ltd. 1952.

The Threshold of the Abnormal. A Basic Survey of Psychopathology. By Werner Wolff. (Pp. 473. 30*s*.) London : Medical Publications Ltd. 1952.

Hemifacial Spasm. A Clinical and Pathophysiological Study. By Robert Wartenberg. (Pp. 86 ; 27 illustrations. $4.00.) New York : Oxford University Press. 1952.

Livre Jubilaire. By Groupement Belge d'Études oto-neuro-ophtalmologiques et neuro-chirurgicales. (Pp. 705 ; 126 text-figures, 21 plates. B. francs 350.00.) Brussels : Journal Belge de Neurologie et de Psychiatrie. 1951.

Gehirnschnitt Modell. By Eduard Weber. (18 figures. DM. 4.20.) Munich : Urban and Schwarzenberg.

Electroencephalography in Clinical Practice. By Robert S. Schwab. (Pp. 195 ; 106 figures. 32*s*. 6*d*.) London : W. B. Saunders. 1951.

Fundamentals of Neurology. 2nd edition. By Ernest Gardner. (Pp. 336 plus index ; illustrated. 24*s*.) London : W. B. Saunders. 1952.

Psychoanalysis : Evolution and Development. By Clara Thompson, with the collaboration of Patrick Mullahy. (Pp. 252. 18*s*.) London : George Allen and Unwin. 1952.

Die Zerebrale Angiographie. By H. Krayenbuhl and Hs. R. Richter. (Pp. 213; 100 illustrations. DM. 59.70.) Stuttgart: Georg Thieme. 1952.

Angst und Schreck. By Friedrich Panse. (Pp. 189; 4 illustrations. DM. 12.60.) Stuttgart: Georg Thieme. 1952.

INTERNATIONAL CONGRESS OF NEUROLOGY, 1953

The fifth international congress of neurology will be held in Lisbon from September 7 to 12, 1953. This will be followed by a meeting in Madrid to commemorate the anniversary of the birth of Ramón y Cajal.

The General Secretary of the Congress is Dr. Almeida Lima of Lisbon, and the National Committee for Great Britain will be: Vice-President, Dr. F. M. R. Walshe; Secretary, Mr. Harvey Jackson; Treasurer, Dr. Wm. Gooddy.

The Executive Committee selected three topics for the symposia of the Congress. Special attention will be paid to the neurosurgical aspects of these subjects. The subject of each symposium, and the persons entrusted with the preparation of the programme for these special topics are as follows: cerebro-vascular conditions (two sessions), Drs. Egas Moniz and Alajouanine; the parietal lobe, Dr. F. M. R. Walshe; metabolic diseases of the nervous system, Dr. L. van Bogaert.

Individual members of the Congress may take part in the discussion of one of these topics, provided application is made beforehand to the General Secretary, and a résumé of the proposed communication sent to him not later than February 1, 1953. Five minutes will be allowed for such a communication.

Afternoon sessions will be arranged for the presentation of papers on various subjects. The time limit for individual papers will be 10 minutes. Members who wish to read a paper should apply to the Secretary of the National Committee to whom a summary of the proposed communication must be submitted not later than November 1, 1952. No Member may make more than one personal communication.

There are three categories of membership of the Congress:

(1) *Active Members:* Neurologists, neurosurgeons, psychiatrists, neuropathologists, and electro-encephalographers. **Fee: £5 0s. 0d.**

(2) *Associate Members:* Other medical or scientific workers interested in neurology. **Fee: £3 10s. 0d.**

(3) *Adjunct Members:* Lay persons and members of the families of active members who are interested in the Congress may apply for adjunct membership. **Fee: £2 0s. 0d.**

Application for membership in any category should be made to the Secretary of the National Committee, Mr. Harvey Jackson, The National Hospital, Queen Square, London, W.C.1. Fees will be payable on completion of the application form.

The official languages of the Congress will be English, French, Spanish, Italian, and Portuguese. Summaries of papers should be submitted in English or French.

The official travel agents for the Congress will be the American Express Agency.

THE MAY (1952) ISSUE

The May (1952) issue contains the following papers:—

Ablation of Abnormal Cortex in Cerebral Palsy. By Wilder Penfield.

The Efferent Fibres of the Hippocampus in the Monkey. By D. A. Simpson.

Studies in Traumatic Epilepsy. Part I: Factors Influencing the Incidence of Epilepsy after Brain Wounds. By W. Ritchie Russell and C. W. M. Whitty.

Wounds of the Visual Pathway. Part I: The Visual Radiation. By J. M. K. Spalding.

Rapid Serial Angiography: Further Experience. By Peter H. Schurr and Ingmar Wickbom.

Chronic Neurological Disease as a Possible Form of Lead Poisoning. By E. J. Butler.

The Action of Decamethonium Iodide (C 10) in Myasthenia Gravis. By H. C. Churchill-Davidson and A. T. Richardson.

Case Report: Reflex Epilepsy and Peripheral Injury. By J. W. Rae.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.